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Tetrabromophenolphthalein ethyl ester (potassium salt) is an indicator that has been put to a novel purpose. Its exceptionally great ' protein error ' affords a method for the detection of proteins. See F. Feigl, **Spot Tests,** Vol. 2, p. 293. Elsevier Publishing Company (1954). The indicator has recently become available under H. & W. Code 8439.

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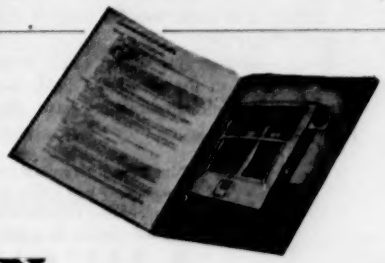

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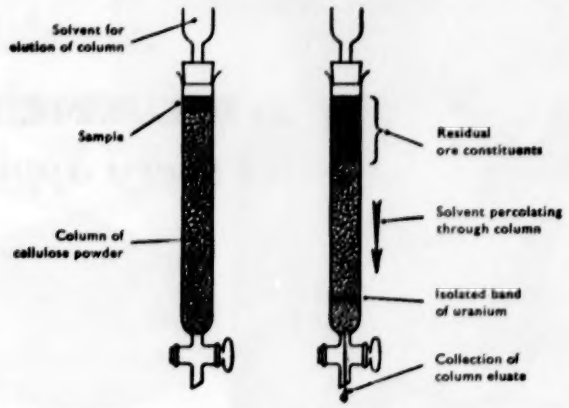

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This report of a Symposium held in London on 2nd February, 1956, is the fourth in The Chemical Society's series of Special Publications. The following are the main contributions:

"Steric Effects in Azo and Indigo Dyes," by Wallace R. Brode (Washington).

"*cis-trans*-Isomerism in Azo-dyes," by E. Atherton and R. H. Peters.

"Synthesis of Azaporphins and Related Macrocycles," by J. A. Elvidge (Imperial College).

"Synthetic Carotenoids," by O. Isler, H. Lindlar, M. Montavon, R. Rüegg, G. Saucy, and P. Zeller (Basle).

"Modern Theories of Colour," by M. J. S. Dewar (London).

In addition to the above papers, much information is given in the report of the discussion, which is included in the publication.

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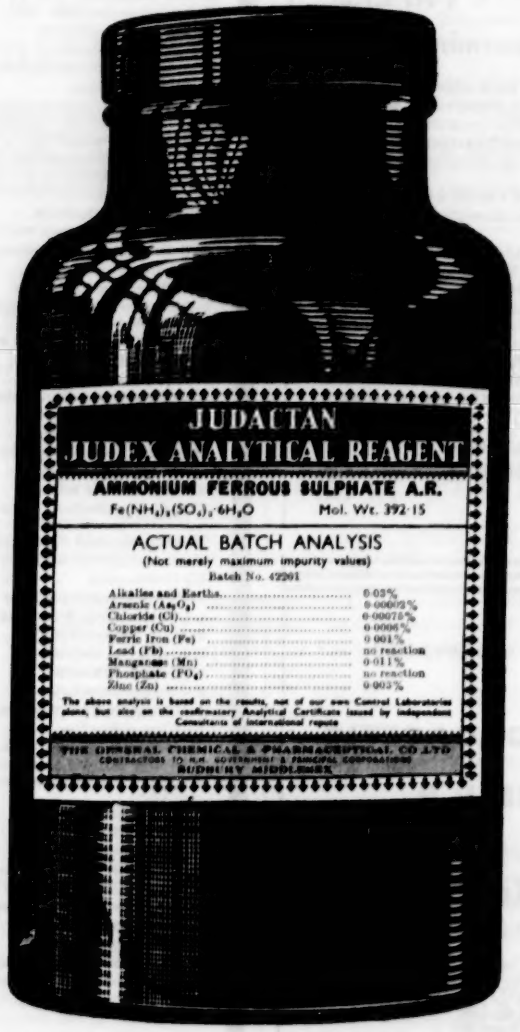
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781. *Unsaturated Fatty Acids. Part II.* The Synthesis of Linolenic Acid.†*

By S. S. Nigam and B. C. L. Weedon.

The first synthetical confirmation of the long-accepted structure of linolenic acid is presented.

Condensation of 1-bromo-octa-2 : 5-diyne (prepared from 1-bromopent-2-yne and propargyl alcohol) with the Grignard reagent of the ethylene acetal of dec-9-ynal (prepared from dec-9-ynoic acid) gave the triacetylenic acetal (IX). This was converted by partial hydrogenation, bromination, hydrolysis, and oxidation, into the solid 9 : 10 : 12 : 13 : 15 : 16-hexabromostearic acid from which it is known that linolenic acid can be regenerated.

An important class of natural acids contains unsaturated centres separated by a methylene group. Unsaturated systems of this type are highly reactive; they rearrange readily in the presence of alkalis, and autoxidise with great ease on exposure to air. The most familiar of these acids with "methylene interrupted conjugation" are the diene linoleic (octadeca-9 : 12-dienoic) acid and the triene linolenic (octadeca-9 : 12 : 15-trienoic) acid.[1] Several related compounds are also known, and acids with up to six methylene-separated double bonds have been reported. These occur mainly in brain and liver phosphatides, and in fish-liver oils.[2] Of the natural acids with methylene-interrupted conjugation only linoleic, the simplest member of the series, has previously been synthesised.[3-5] A synthetical confirmation of the structure (XII) assigned to linolenic acid on the basis of degradative studies is described in this paper.

Linolenic acid is the most abundant and widespread triene acid in Nature. It occurs principally in the vegetable drying oils, and is largely responsible for the ease with which these harden on exposure to air. It is usually isolated from linseed oil, in which it may comprise 50% or more of the total acids present,[1] as a solid hexabromide. This on debromination with zinc [7] gives "α-linolenic acid" which has been used in most investigations and structural studies. Although originally thought to be identical with the natural compound, the α-acid has been shown to contain small amounts of isomers.[8,9] These artefacts can, however, be removed by low-temperature crystallisation.[8] As linolenic acid is an unstable liquid, the present studies were aimed at the synthesis of the solid hexabromide.

One of the two key intermediates required, the nonynyldioxolan (III), has previously been prepared from deca-1 : 9-diyne by Walborsky, Davies, and Howton.[4] A convenient alternative route has now been developed which avoids the use of sulphur compounds, and hence the risk of catalyst poisoning in subsequent hydrogenations of materials prepared from the nonynyldioxolan. The readily-available dec-9-ynoic acid (I) [10] was converted into its *N*-methylanilide, which was reduced with lithium aluminium hydride [11] to dec-9-ynal (II). Reaction of the latter with ethylene glycol then gave the nonynyldioxolan (III) in 40% overall yield.

* Part I, *J.*, 1953, 1785.

† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Hilditch, "The Chemical Constitution of Natural Fats," Chapman and Hall, London, 1956.

[2] Klenk and Bongard, *Z. physiol. Chem.*, 1952, **291**, 104; Klenk and Lindlar, *ibid.*, 1955, **299**, 74; 1955, **301**, 156; Klenk and Dreike, *ibid.*, 1955, **300**, 113; Silk and Hahn, *Biochem. J.*, 1954, **57**, 582.

[3] Raphael and Sondheimer, *J.*, 1950, 2100.

[4] Walborsky, Davies, and Howton, *J. Amer. Chem. Soc.*, 1951, **73**, 2590.

[5] Gensler and Thomas, *ibid.*, p. 4601.

[6] Erdmann, Bedford, and Raspe, *Ber.*, 1909, **42**, 1334.

[7] Rollett, *Z. physiol. Chem.*, 1909, **62**, 422; McCutcheon, *Org. Synth.*, 1942, **22**, 82.

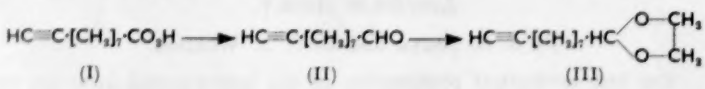
[8] Matthews, Brode, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 1064.

[9] McCutcheon, Crawford, and Welsh, *Oil and Soap*, 1941, **18**, 9; Ahlers, Brett, and McTaggart, *J. Appl. Chem.*, 1953, **3**, 433.

[10] Black and Weedon, *J.*, 1953, 1785.

[11] Weygand and Eberhardt, *Angew. Chem.*, 1952, **64**, 458; Weygand, Eberhardt, Linden, Schäfer, and Eigen, *ibid.*, 1953, **65**, 525; Weygand and Mitgau, *Chem. Ber.*, 1955, **88**, 301; Nigam and Weedon, to be published.

As second component a 1-halogeno-octa-2 : 5-diyne was required. Reaction of the Grignard reagent of but-1-yne [12] with an excess of 1 : 4-dichlorobut-2-yne [13] gave 1-chloro-



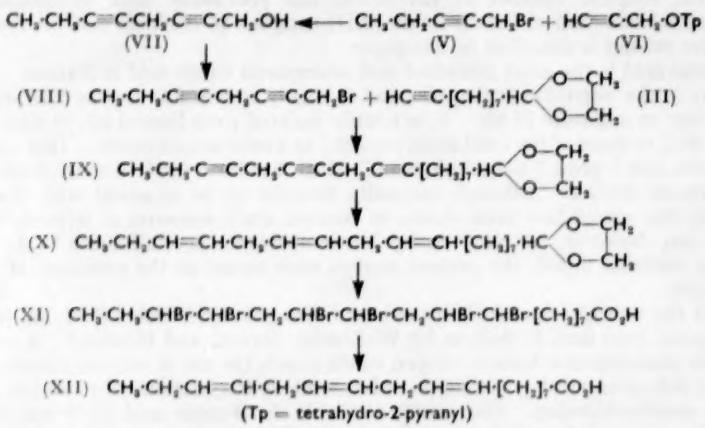
(I) (II) (III)

octa-2 : 5-diyne (IV) in 11% yield. (A cuprous chloride catalyst [14] was used in this and subsequent condensations of Grignard reagents with acetylenic halides.) An attempt

(IV)

to cause the chloride to react with the Grignard reagent of the nonynyldioxolan gave only traces of the required product. Attention was therefore directed to the corresponding bromide which was prepared in the following way.

Condensation of 1-bromopent-2-yne (V) [15] with the Grignard reagent of the tetrahydropyranyl ether (VI) [16] derived from propargyl alcohol, and alcoholysis [17] of the initial product, gave octa-2 : 5-diyn-1-ol (VII) (α-naphthylurethane) in 50% overall yield. (Deca-2 : 5-diyn-1-ol was similarly prepared from 1-bromohept-2-yne.[5, 18]) The structure of the octadiynol, an acetylenic alcohol of new type, was confirmed by its light-absorption properties, and by catalytic reduction to octan-1-ol (88%). Treatment of the octadiynol with phosphorus tribromide gave (58%) 1-bromo-octa-2 : 5-diyne (VIII).



(VII) (V) (VI)

(VIII) (III)

(IX)

(X)

(XI)

(XII)

(Tp = tetrahydro-2-pyranyl)

A Grignard condensation of the two intermediates (III) and (VIII) gave the triyne (IX) (2 : 4-dinitrophenylhydrazone) in 33% yield. Partial reduction over Lindlar catalyst [19] then led to the corresponding triene (X). From the known stereochemical course of reductions with this catalyst,[20] the triene was assumed to consist mainly, if not exclusively, of the " all-*cis* " isomer, and thus to have the same configuration as that assigned to linolenic acid on the basis of Raman and infrared absorption studies.[9]

Bromination of the triene produced a mixture of bromo-acetals, which was converted

[12] Aston, Mastrangelo, and Moessen, *J. Amer. Chem. Soc.*, 1950, **72**, 5287.
[13] Johnson, *J.*, 1946, 1009.
[14] Danehy, Killian, and Nieuwland, *J. Amer. Chem. Soc.*, 1936, **58**, 611; Nigam and Weedon, to be published.
[15] Tchao Yin Lai, *Bull. Soc. chim. France*, 1933, **53**, 1533.
[16] Henbest, Jones, and Wells, *J.*, 1950, 3646.
[17] Ahmad and Weedon, *J.*, 1953, 3286; Dauben and Bradlow, *J. Amer. Chem. Soc.*, 1952, **74**, 559.
[18] Wotiz, *ibid.*, 1950, **72**, 1639.
[19] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[20] Baker, Linstead, and Weedon, *J.*, 1955, 2218.

by hydrolysis and oxidation into a mixture of hexabromostearic acids (XI) in 50% overall yield. Bromination of linolenic acid gives a similar mixture of hexabromo-acids, from which one of the four possible racemates can be isolated as a solid in *ca.* 25% yield.[21] Crystallisation of the synthetic mixture gave the same solid in 16% yield. The identity was confirmed by direct comparison of the acid and its methyl ester with authentic samples derived from natural linolenic acid. No depressions were observed in the mixed melting point determinations, and the infrared absorption spectra were identical. Since, as mentioned above, the solid hexabromide can be converted into linolenic acid (XII) by debromination and low-temperature crystallisation,[8] the results now reported constitute a formal synthesis of this natural acid.

Experimental

M. p.s were determined on a Kofler block and are corrected.

Ultraviolet light absorption measurements were determined on alcoholic solutions. Infrared absorption measurements were made on liquid films, unless stated otherwise.

All operations were carried out in an inert atmosphere, usually of nitrogen. Freshly purified solvents were used to ensure the absence of peroxides. Tetrahydrofuran was dried over solid potassium hydroxide and then over sodium wire, and was redistilled immediately before use. Compounds containing methylene-interrupted conjugation were used as soon as possible after preparation, to minimise the losses due to polymerisation and oxidation.

To ensure the absence of ethyl bromide in the copper-catalysed Grignard reactions, a slight excess of magnesium was used in the preparations of ethylmagnesium bromide, and the resulting solutions were decanted from the excess of metal.

Intermediates.—1-Bromopent-2-yne [18] was prepared from but-1-yne [12] *via* pent-2-yn-1-ol.[22] Infrared absorption: maxima, 4·320 and 4·460 μ (for C≡C); no allene band was observed. The pentynol *α-naphthylurethane* crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 109° (Found: C, 75·35; H, 6·2; N, 5·65. $C_{14}H_{15}O_2N$ requires C, 75·85; H, 5·95; N, 5·55%).

1-Bromohept-2-yne [5,19] was prepared similarly from hex-1-yne. Hept-2-yn-1-yl methanesulphonate was prepared by the method of Raphael and Sondheimer,[3] and 1 : 4-dichlorobut-2-yne by that of Johnson.[4]

Dec-9-ynoic acid [10] was prepared from commercial undec-10-enoic acid. The latter was converted into undec-10-ynoic acid in 80% yield by Khan's method,[23] and thence in 74% yield into 1 : 1-diphenylundec-1-en-10-yne [10] which crystallised from *n*-pentane and had m. p. 35°. Chromic acid oxidation of the hydrocarbon gave dec-9-ynoic acid, m. p. 22°, in 58% yield, and a neutral fraction (*ca.* 20%). The latter partly solidified; recrystallisation from light petroleum (b. p. 40—60°) gave a material, m. p. 112—113°. Infrared light absorption: maxima 2·86, 3·08 (OH), 5·835 (CO), 6·23, 13·38, and 14·32 μ (Ph). Oxidation of the solid with periodic acid gave benzophenone, which was isolated in 30% yield as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 238°.

2-Non-8′-ynyl-1 : *3-dioxolan* (III).— A solution of dec-9-ynoic acid (23·7 g.) in thionyl chloride (48 c.c.) was heated under reflux until the evolution of hydrogen chloride ceased, and then evaporated. Distillation of the residue gave the acid chloride (22·5 g., 86%), b. p. 58—64°/0·1 mm., n_D^{21} 1·4610.

A solution of methylaniline (16·1 g.) in an equal volume of pyridine was slowly added to one of the acid chloride in benzene (90 c.c.) cooled in an ice-bath. The mixture was shaken occasionally and kept at 20° for ½ hr. Water was added, and the product was extracted with benzene. The extract was washed thoroughly with 2N-hydrochloric acid and then with water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the *methylanilide* (26·4 g., 85%), b. p. 155—165° (bath temp.)/10^{-4} mm., n_D^{22} 1·5190 (Found: C, 78·8; H, 8·85; N, 5·55. $C_{17}H_{23}ON$ requires C, 79·35; H, 9·0; N, 5·45%).

A solution of lithium aluminium hydride (1·53 g.) in ether (150 c.c.) was added slowly to a cooled (0°) and well-stirred solution of the methylanilide (21 g.) in ether (150 c.c.). After the mixture had been stirred at 0° for 3 hr., a small volume of ethyl acetate was added (to decompose the excess of hydride), followed by 2N-hydrochloric acid. The product was extracted with ether and the extract was washed thoroughly with 2N-hydrochloric acid and then with water,

[21] Shinowara and Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 2734.
[22] Tchao Yin Lai, *Bull. Soc. chim. France*, 1933, **53**, 682.
[23] Khan, *Org. Synth.*, 1952, **32**, 104.

dried (Na_2SO_4), and evaporated, giving crude dec-9-ynal (10·5 g.). The 2 : 4-dinitrophenylhydrazone crystallised in golden-yellow plates, m. p. 73·5°, undepressed on admixture with the specimen described below.

A mixture of the crude aldehyde (3·5 g.), benzene (100 c.c.), ethylene glycol (30 c.c.), and concentrated sulphuric acid (2 drops) was stirred vigorously and heated under reflux for 4·5 hr., the water formed being removed by azeotropic distillation. The mixture was cooled and diluted with 5% aqueous sodium hydroxide. The benzene layer was separated, washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 2-non-8′-ynyl-1 : 3-dioxolan (2·9 g.), b. p. 120—122°/8 mm., n_D^{22} 1·4570 (Found : C, 73·95; H, 10·55. Calc. for $C_{12}H_{20}O_2$: C, 73·45; H, 10·25%). Treatment with Brady's reagent gave a 2 : 4-dinitrophenylhydrazone, m. p. 73·5° undepressed on admixture with the derivative from a specimen of the acetal prepared by the method of Walborsky, Davies, and Howton [4] (who give m. p. 73—74°).

1-*Chloro-octa*-2 : 5-*diyne* (IV).—A solution of 1 : 4-dichlorobut-2-yne [12] (74 g.) in ether (50 c.c.) was added slowly to a cooled (0°), well-stirred ethereal solution (125 c.c.) of butynylmagnesium bromide [prepared from magnesium (6·1 g.), ethyl bromide (21·8 g.), and but-1-yne (19 g.)], containing cuprous chloride (0·75 g.). The mixture was stirred at 20° overnight, and then under reflux for 8 hr. The mixture was cooled, 2N-hydrochloric acid was added, and the product was isolated with ether. Distillation gave 1 : 4-dichlorobut-2-yne (53 g.), and 1-*chloro-octa*-2 : 5-*diyne* (3 g.), b. p. 42—44°/10^{-2} mm., n_D^{15} 1·4985 (Found : C, 68·25; H, 6·6; Cl, 25·65. C_8H_9Cl requires C, 68·35; H, 6·4; Cl, 25·25%. Hydrogen number, 29·7; equivalent to 4·7 double bonds). Ultraviolet light absorption : no maximum with $E_{1\,cm.}^{1\%}$ >20 in the region 200—400 mμ. Infrared light absorption : maxima, 4·310, 4·375, 4·440 (for C≡C), 5·135 μ (allenic impurity).

The chloro-octadiyne (2·8 g.), the Grignard reagent of 2-non-8′-ynyl-1 : 3-dioxolan (3·7 g.), and cuprous chloride (0·25 g.) in ether (50 c.c.) were stirred at 20° overnight, and then under reflux for 18 hr. Isolation of the product in the usual way gave an oil (4·3 g.). To determine whether this contained any of the highly unstable triacetylene (IX), it was hydrogenated in ethyl acetate over Adams catalyst, and the product was examined for a derivative of octadecanal. Distillation gave : (i) 2-*Nonyl*-1 : 3-*dioxolan* (1·4 g.), b. p. 68—70°/10^{-2} mm., n_D^{22} 1·4390 (Found : C, 72·0; H, 12·2. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·1%). Treatment with Brady's reagent yielded decanal 2 : 4-dinitrophenylhydrazone, m. p. 108° undepressed on admixture with an authentic specimen prepared from decanoic acid ; [11] (ii) A fraction (0·15 g.), b. p. 175—180° (bath temp.)/10^{-2} mm., which with Brady's reagent gave a crude derivative (80%). This, after chromatography from benzene on bentonite–kieselguhr, and crystallisation from alcohol, yielded (52%) a solid, m. p. 108° undepressed on admixture with a specimen, m. p. 110°, of octadecanal 2 : 4-dinitrophenylhydrazone prepared from stearic acid.[11] At this stage the route described below to 1-bromo-octa-2 : 5-diyne was developed, and further work with the chloro-octadiyne was abandoned.

Octa-2 : 5-*diyn*-1-*ol* (VII).—A solution of ethylmagnesium bromide was prepared in ether (50 c.c.), from magnesium (3·6 g.) and ethyl bromide (15 g.), and was then diluted with tetrahydrofuran (130 c.c.). Tetrahydro-2-prop-2′-ynyloxypyran [14] (21 g.), dissolved in tetrahydrofuran (50 c.c.), was added slowly to the well-stirred solution of the Grignard reagent. The mixture was boiled under reflux for 3 hr., cooled to 20°, and then cuprous chloride (0·36 g.) was added. After the mixture had been stirred for 15 min., 1-bromopent-2-yne [15] (20·3 g.) in tetrahydrofuran was added dropwise. Stirring was continued for 3 hr. at 20° and then for 16 hr. under reflux. After the mixture had been cooled to 0°, an excess of saturated ammonium chloride solution was added, and the product was isolated with ether. The ethereal extract was washed thoroughly with water, dried (K_2CO_3), and evaporated. The residue (32·1 g.) was dissolved in alcohol (170 c.c.), toluene-*p*-sulphonic acid (1·1 g.) was added, and the solution was boiled under reflux for 2·5 hr., then cooled, and diluted with water. The product was extracted with ether, and the extract washed with saturated sodium hydrogen carbonate solution then with water, dried (K_2CO_3), and evaporated. Distillation of the residue gave *octa*-2 : 5-*diyn*-1-*ol* (8·5 g.), b. p. 68°/10^{-3} mm., n_D^{24} 1·4900 (Found : C, 78·3; H, 8·45. $C_8H_{10}O$ requires C, 78·65; H, 8·25%. Hydrogen number, 29·2; equivalent to 4·2 double bonds). Ultraviolet light absorption : maximum at 262 mμ, $E_{1\,cm.}^{1\%}$ 6, suggesting the presence of a trace of an impurity with a dienyne chromophore. Infrared light absorption : maxima, 3·095 (OH), 4·360, 4·410, 4·480 (C≡C), 7·585 and 9·860 μ (OH and C–O) ; no allene band was observed. The α-*naphthylurethane* (*ca.* 90% yield), crystallised from light petroleum (b. p. 80—100°) and had m. p. 126° (Found : C, 78·05; H, 6·15; N, 4·95. $C_{18}H_{17}O_2N$ requires C, 78·35; H, 5·9; N, 4·8%).

Reduction of the alcohol (1·1 g.) in ethyl acetate (30 c.c.) over Adams catalyst, and isolation of the product in the usual way, gave octan-1-ol (1·02 g.), b. p. 92°/12 mm., n_D^{24} 1·4290. The α-naphthylurethane (*ca.* 90% yield) crystallised from light petroleum (b. p. 80—100°) in needles, m. p. and mixed m. p. 66° (Adamson and Kenner [25] give m. p. 66°).

Deca-2 : 5-diyn-1-ol.—(*a*) Condensation of 1-bromohept-2-yne [5, 18] with the Grignard reagent of tetrahydro-2-prop-2′-ynylpyran, and alcoholysis of the initial product, gave deca-2 : 5-diyn-1-ol (33%) as a very unstable liquid, b. p. 86°/10^{-3} mm., n_D^{21} 1·4860. Ultraviolet light absorption : maximum, 266 mμ, $E_{1\,cm.}^{1\%}$ 18. Infrared light absorption : maxima at 3·020, 4·415, 4·480, 7·630, and 9·855 μ. The *α-naphthylurethane* (75% yield) crystallised from light petroleum (b. p. 80—100°) and had m. p. 102° (Found : C, 79·3; H, 7·0; N, 4·6. $C_{21}H_{21}O_2N$ requires C, 78·95; H, 6·65; N, 4·4%). Catalytic hydrogenation of the alcohol gave decan-1-ol (70%)[α-naphthylurethane, m. p. and mixed m. p. 71° (Talvitie [26] gives m. p. 71·4°)].

(*b*) A solution of the Grignard reagent of tetrahydro-2-prop-2′-ynyloxypyran [from magnesium (0·7 g.) and the acetylene (4·2 g.)] in tetrahydrofuran (70 c.c.) was added during 2 hr. to a well-stirred, boiling solution of hept-2-ynyl methanesulphonate [3] (11·6 g.) in the same solvent (125 c.c.). The resulting suspension was heated under reflux for 16 hr. and then cooled. An excess of 2N-sulphuric acid was added, and the mixture was stirred vigorously for 30 min. Isolation of the product with ether and distillation gave : (i) 1-Bromohept-2-yne (4·3 g., 80%) and (ii) crude deca-2 : 5-diyn-1-ol (3 g., 65%), n_D^{21} 1·4720. The α-naphthylurethane (40% yield) and its mixture with a specimen from (*a*), both had m. p. 102°.

1-Bromo-octa-2 : 5-diyne (VIII).—Phosphorus tribromide (5·7 g.) was added to a stirred solution of octa-2 : 5-diyn-1-ol (7·1 g.) and pyridine (0·11 g.) in ether (30 c.c.) at such a rate that the mixture boiled gently. The mixture was heated under reflux for a further 3 hr. and then cooled. The upper layer was decanted on ice, and the product was extracted with ether. The extract was washed with saturated sodium carbonate solution, dried ($CaCl_2$), and evaporated. Distillation of the residue gave *1-bromo-octa-2 : 5-diyne* (6·3 g.), b. p. 50—52°/10^{-4} mm., n_D^{24} 1·5250 (Found : C, 51·35; H, 5·1. C_8H_9Br requires C, 51·9; H, 4·9%). Ultraviolet light absorption : maxima, 216 and 290 mμ, $E_{1\,cm.}^{1\%}$ 70 and 4, respectively. Infrared light absorption : maxima, 4·395, 4·463 (C≡C) and 5·155 μ (allenic impurity).

2-(Heptadeca-8 : 11 : 14-triynyl)-1 : 3-dioxolan (IX).—A well-stirred solution of ethylmagnesium bromide [from magnesium (0·6 g.) and ethyl bromide (2·5 g.)] in ether (25 c.c.) was diluted with tetrahydrofuran (65 c.c.), and a solution of 2-8′-nonynyl-1 : 3-dioxolan (5·0 g.) in tetrahydrofuran (25 c.c.) was added slowly. The mixture was stirred vigorously at 20° for 4 hr., and then under reflux for 1·5 hr. The resulting acetylenic Grignard solution was cooled and added during 2 hr. to a warm (35°), vigorously-stirred mixture of 1-bromo-octa-2 : 5-diyne (4·3 g.), tetrahydrofuran (75 c.c.), and cuprous chloride (0·25 g.). The mixture was boiled for 16 hr., more cuprous chloride (0·25 g.) being added after 10 hr., and then cooled. Water was added, the inorganic salts were removed by filtration, and the product was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue from a short-path still gave (i) a mixture of starting materials and (ii) the tri-yne (2·3 g., 33%), b. p. 165—175° (bath temp.)/10^{-5} mm. The product was very unstable, and no attempt was made to analyse it. On treatment with Brady's reagent it gave *octadeca-9 : 12 : 15-triynal 2 : 4-dinitrophenylhydrazone* (*ca.* 80%), which crystallised from alcohol and had m. p. 102° (Found : N, 13·25. $C_{24}H_{32}O_4N_4$ requires N, 12·85%).

When the reaction mixture was refluxed for only 5 hr., the yield of the tri-yne was reduced to 7%.

9 : 10 : 12 : 13 : 15 : 16-Hexabromostearic Acid (XI).—A solution of the tri-yne (2·3 g.), freshly distilled, in *n*-hexane (100 c.c.) was shaken in hydrogen in the presence of Lindlar catalyst (2·3 g.) until there was a marked diminution in rate of absorption (400 c.c. of hydrogen were taken up at 17°/763 mm., equivalent to 73% of the theoretical for 3 mol.; this low figure is attributed to loss of material by polymerisation). The catalyst was filtered off, and a solution of bromine (4 g.) in *n*-hexane (4 c.c.) was added dropwise until a permanent red coloration indicated a slight excess of bromine. The solution was kept at 0° overnight, and then shaken with 10% aqueous sodium thiosulphate (to remove excess of bromine), with dilute sodium carbonate, and finally with water. The solution was dried (Na_2SO_4) and evaporated, giving a viscous residue (4·2 g.) which deposited a small amount of a solid.

To a warm (55—60°), well-stirred solution of the crude product in glacial acetic acid (120

[24] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.
[25] Adamson and Kenner, *J.*, 1934, 838.
[26] Talvitie, *Ann. Acad. Sci. Fennicae*, 1927, **26**, *A*, 1.

c.c.), a solution of chromium trioxide (2·2 g.) in 2N-sulphuric acid (40 c.c.) was added dropwise. The mixture was stirred at 20° overnight, and then concentrated to a small volume under reduced pressure. 2N-Sulphuric acid (130 c.c.) was added. The mixture was warmed (steam-bath) for 1 hr., then cooled, diluted with saturated brine (95 c.c.), and extracted with chloroform. Evaporation of the extract gave a mixture of bromo-acids (3 g.) which was extracted with light petroleum (b. p. 80—100°). The residual solid (0·5 g., 16%) had m. p. 177°. Extraction with benzene and crystallisation from dioxan yielded 9 : 10 : 12 : 13 : 15 : 16-hexabromostearic acid, m. p. 181—182°, undepressed on admixture with the solid hexabromide, m. p. 181—182°, prepared from natural linolenic acid (Rollett [7] gives m. p. 180—181°). The infrared spectra of Nujol mulls of the " natural " and the synthetic acid were identical.

In another experiment the mixture of bromo-acids was esterified in ethereal suspension with diazomethane. Chromatography of the methyl esters on alumina (Savory and Moore), pentane–ether being used as eluant,[27] and crystallisation from alcohol, gave (10%) methyl 9 : 10 : 12 : 13 : 15 : 16-hexabromostearate, m. p. 157—158°, undepressed on admixture with a specimen from natural linolenic acid (Stanfield and Schierz [28] give m. p. 157—158°). The infrared spectra of carbon tetrachloride solutions of the " natural " and the synthetic ester were identical. No lower or higher bromo-stearates were detected in the chromatogram. Model experiments showed that methyl tetra- and hexa-bromostearate are readily separated on alumina, but that the recovery of each ester is only *ca.* 50%.

Hydrolysis of methyl hexabromostearate for ½ hr. in a boiling mixture (1 : 5) of 2N-hydrochloric acid and dioxan, and evaporation of the resulting solution gave (90%) a solid, m. p. 180°. Recrystallisation from dioxan gave hexabromostearic acid, m. p. and mixed m. p. 181—182°.

The authors are indebted to Dr. A. H. Hosking for an authentic sample of linolenic acid hexabromide. One of them (S. S. N.) thanks the University of Saugar, India, for study leave. Microanalyses and spectral measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic laboratories (Mrs. A. I. Boston, Mr. R. L. Erskine) of this Department.

A brief account of some of the work described in this paper has been published previously.[29]

Department of Chemistry, Imperial College of Science and Technology,
South Kensington, London, S.W.7. [*Received, March 24th*, 1956.]

[27] Howton, *Science*, 1955, **121**, 704.
[28] Stanfield and Schierz, *J. Amer. Chem. Soc.*, 1932, **54**, 4357.
[29] Nigam and Weedon, *Chem. and Ind.*, 1955, 1555.

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782. *The Dimerisation of Mesityl Oxide. A Novel Type of Diene Addition.**

By (the late) E. A. Braude, B. F. Gofton, G. Lowe, and E. S. Waight.

Mesityl oxide (I) dimerises exothermally under the influence of lithium, to give 2-acetyl-1 : 3 : 3 : 5-tetramethyl*cyclo*hex-5-en-1-ol (II) besides other products. The reaction can be regarded as a diene addition between the enolate (Ia), formed on the metal surface and acting as diene, and the ketone (I) acting as dienophil. The structure of the dimer (II), which contains a highly hindered carbonyl group, has been deduced from spectroscopic evidence and degradative reactions, including conversion into 2 : 3 : 4 : 6-tetramethylacetophenone (XI).

The work described in this paper arose from the observation [1] that the reaction of mesityl oxide with *iso*butenyl-lithium yields, besides the expected alcohol, a high-boiling, crystalline product, m. p. 73°. This compound showed no high-intensity light absorption in the near-ultraviolet and did not yield a 2 : 4-dinitrophenylhydrazone, and it was at first taken to be a bimolecular reduction product such as has been reported to be formed from mesityl

* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Braude and Coles, *J.*, 1952, 1425.

oxide by the action of magnesium or other metals.[2] A product of this kind might have conceivably arisen by a reducing action of the lithium alkenyl.[3]

The analytical data, however, showed that the compound was a dimer of mesityl oxide and the comparatively large amount obtained suggested that its formation was brought about by a catalytic effect of traces of lithium metal present in the reaction mixture. This was confirmed when it was found that mesityl oxide undergoes an exothermic reaction when added to a suspension of lithium in ether, to give a mixture from which the solid dimer, $C_{12}H_{20}O_2$, identical with that obtained earlier, was isolated. The infrared spectrum of the dimer indicated the presence of a hydroxyl group ($\nu_{max.}$ 3475 cm.$^{-1}$) and of an isolated keto-group ($\nu_{max.}$ 1700 cm.$^{-1}$) which appeared to be intramolecularly hydrogen-bonded since the absorption bands in carbon tetrachloride were sharp and independent of concentration, a behaviour typical of α- and β-, but not of γ-, ketols.[4] The presence of a keto-group was supported by a weak ultraviolet absorption band near 2900 Å, but the failure of the dimer to yield a derivative with Brady's reagent suggested that this group was highly hindered.

Catalytic hydrogenation of the dimer with platinum oxide in ethyl acetate gave a dihydro-derivative which according to the infrared spectrum still contained the intramolecularly hydrogen-bonded hydroxyl and carbonyl functions, indicating that one ethylenic bond was originally present and that the dimer was monocyclic. Catalytic hydrogenation in acetic acid gave a liquid product, $C_{12}H_{22}O$, the infrared spectrum of which indicated the presence of a non-bonded keto-group ($\nu_{max.}$ 1711 cm.$^{-1}$) and the absence of a hydroxyl group; under these conditions, hydrogenolysis as well as saturation of the ethylenic bond had evidently taken place, suggesting that the hydroxyl group was originally in an allylic position and probably tertiary. This was confirmed by the ready dehydration of the dimer when heated with a trace of iodine, which furnished a dehydro-derivative, $C_{12}H_{18}O$, showing ultraviolet absorption characteristic of a conjugated, semicyclic diene ($\lambda_{max.}$ 2360 Å; ε 9000).

At this stage only the position of the carbonyl function relative to that of the ethylenic and hydroxyl groups remained to be established, and a clue to this was provided by dehydration with oxalic acid which, besides the diene obtained above, also yielded a second diene containing a conjugated dienone chromophore ($\lambda_{max.}$ 3020 Å; ε *ca.* 2000). This result showed that the dimer must contain the system C=C·CMe(OH)·CH·CO, giving either C=C·C(=CH_2)·CH·CO or C=C·CMe=C·CO on dehydration.

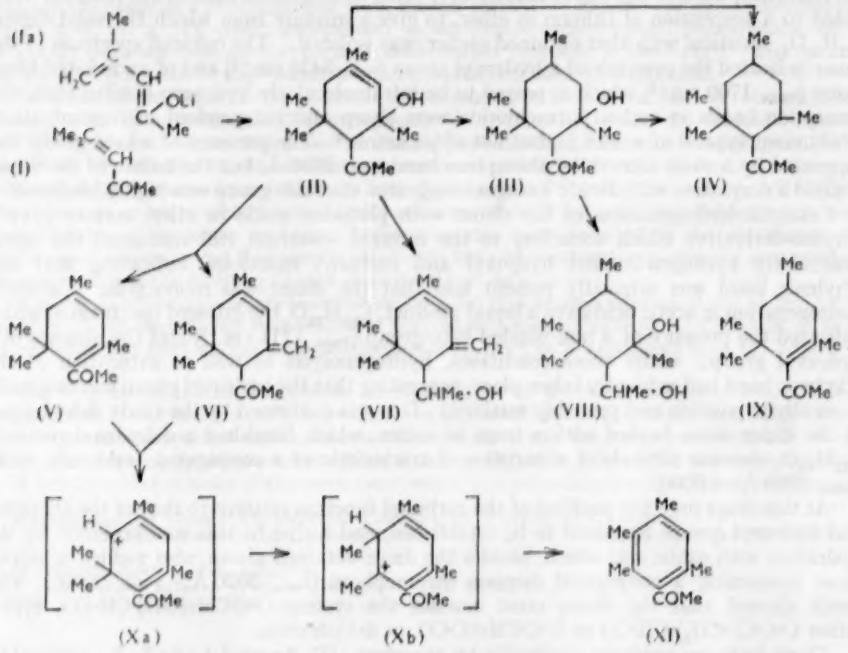
These facts are uniquely explicable by structure (II), 2-acetyl-1 : 3 : 3 : 5-tetramethyl-*cyclo*hex-5-en-1-ol, for the dimer and by the annexed scheme. The presence of an isolated carbonyl group in the dimer (II) was confirmed by reduction with lithium aluminium hydride which was accompanied by dehydration to give the dienol (VII). The dihydro-derivative (III) is similarly reduced to the diol (VIII) but resists dehydration to the unsaturated ketone (IX). It may be noted that the results of "active hydrogen" (Zerewitinoff) determinations proved somewhat misleading in this series; thus, the dimer, with methylmagnesium iodide, evolved methane corresponding to *two* active hydrogen atoms. The hindered acetyl group evidently behaves as an enolic hydroxyl function and this is confirmed by the fact that the ketone (IV) still shows one active hydrogen by this method. (Values corresponding to 0·1—0·5 active hydrogen atom are obtained with other ketones under similar conditions.) The lack of reactivity of the acetyl group towards Brady's reagent is not surprising since it is flanked by four α-substituents in the dimer and by three in the dehydration products; steric hindrance in this system will be even more severe than in 2 : 2 : 6-trimethyl*cyclo*hexanone (which reacts slowly) and 2 : 2 : 6 : 6-tetramethyl*cyclo*hexanone (which does not react under comparable conditions). Similar observations have been made for *o*-methylacetophenones (see below) and other examples

[2] Vogel, *J.*, 1927, 594; Wiemann and Glacet, *Compt. rend.*, 1948, **226**, 923; Glacet, *ibid.*, 1948, **227**, 480; Kolobielski and Wiemann, *ibid.*, 1951, **233**, 691; 1954, **238**, 1039; Kolobielski, *ibid.*, 1953, **237**, 1717; *Ann. Chim.* (*France*), 1955, **10**, 271.

[3] Cf. Braude in "Progress in Organic Chemistry" (J. W. Cook, Ed.), Vol. III, Chapter 4, Butterworths, London, 1955.

[4] Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068; Sheehan, O'Neill, and White, *ibid.*, 1950, **72**, 3376; Duculot, *Compt. rend.*, 1955, **241**, 1738; Lüttke, *Chem. Ber.*, 1950, **83**, 571.

of this type have been described in the steroid field.[5] Steric hindrance is undoubtedly also the cause of the exceptionally weak absorption of the dienone (V) (see above) since the carbonyl group will be prevented from becoming coplanar with the diene system; closely analogous cases are 1-acetyl-2 : 6 : 6-trimethyl*cyclo*hexene [6] and dehydro-β-ionone.[7] It is interesting that the ratios of the ε values for the trialkylated compounds to those found or



expected for the unsubstituted parent compounds are about 0·1 in each case, corresponding [8] to an interplanar angle of 70°. The fact that dehydration of the dimer gives predominantly the exocyclic (VI) rather than the homocyclic dienone (V) provides another indication of the fact that the additional conjugation in the latter is comparatively weak. A preference for systems containing the 1-methyl*cyclo*hex-2-enol grouping as such to undergo exocyclic dehydration has been noted in other cases.[9] Thus Dr. O. H. Wheeler has found that 1 : 3-dimethyl*cyclo*hex-2-en-1-ol with phosphorus oxychloride in pyridine gives 1-methyl-3-methylene*cyclo*hexene showing ultraviolet absorption typical of a semicyclic diene ($\lambda_{max.}$ 2270 Å; ε 9500).*

Structure (II) was confirmed by treatment of the dimer with tetrachloro-1 : 2-benzoquinone, which has been shown [10] to effect aromatisation of *gem.*-alkylated hydroaromatic

* *Added, July 5th*, 1956.—On the other hand, 1 : 3-dimethyl*cyclo*hexa-1 : 3-diene is obtained with sulphuric acid (Meinwald and Grossman, *J. Amer. Chem. Soc.*, 1956, **78**, 992), showing that the course of dehydration depends on the conditions. Interconversion of the dienes, as in the α : β-phellandrene system, may also occur and this matter is being investigated further.

[5] Ruzicka, Jeger, Grob, and Hösli, *Helv. Chim. Acta*, 1943, **26**, 2283; Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571; Elks, Evans, Long, and Thomas, *J.*, 1954, 451.

[6] Henbest and Woods, *J.*, 1952, 1150; Braude and Timmons, *J.*, 1955, 3766.

[7] Henbest, *J.*, 1951, 1074.

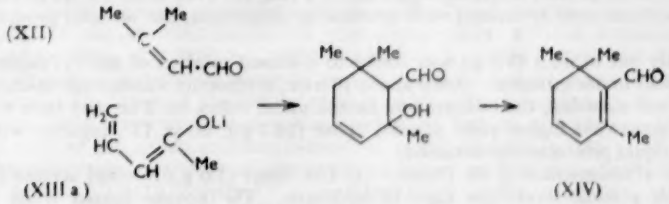
[8] Braude, *Experientia*, 1955, **11**, 457; Braude and Sondheimer, *J.*, 1955, 3754; Braude and Timmons, *J.*, 1955, 3766.

[9] Bann, Heilbron, and Spring, *J.*, 1936, 1274; Mukherji and Bhattacharyya, *J. Amer. Chem. Soc.*, 1953, **75**, 4698; cf. Novello, Christy, and Sprague, *ibid.*, 1954, **76**, 738.

[10] Beames, Braude, Jackman, and Linstead, *Chem. and Ind.*, 1954, 1174; Braude, Linstead, and Lowe, unpublished work.

systems with 1 : 2 migration, rather than loss, of one of the substituents. 2 : 3 : 4 : 6-Tetramethylacetophenone (XI), identical in infrared absorption with a specimen prepared by acetylation of *iso*durene, was obtained in 59% yield; the course of the reaction probably involves initial dehydration to the dienes (V) and (VI), followed by dehydrogenation *via* the unstable carbonium-ion intermediates (Xa and b). Since the ketone (XI) is a liquid and, like the dimer (II), does not easily yield carbonyl derivatives owing to steric hindrance,[11] its identity was confirmed by oxidation to 2 : 3 : 4 : 6-tetramethylbenzoic acid. The strong steric hindrance in 2 : 3 : 4 : 6-tetramethylacetophenone is borne out by the ultraviolet light absorption ($\lambda_{infl.}$ 2450 Å; ε 2000; cf. acetophenone,[8] $\lambda_{max.}$ 2430 Å, ε 13,000); the interplanar angle between the phenyl and the carbonyl group indicated by these data is about 70°, as for the dienone (V) (see above).

It seems highly probable that formation of the dimer (II) involves a diene addition between one molecule of mesityl oxide (I), acting as dienophil, and another in the form of the enolate (Ia), acting as diene. The characteristics of the reaction, which shows an



induction period until the lithium assumes a bright, metallic appearance, suggest that the dimerisation takes place at the metal surface and that the enolate is produced by chemisorption of the ketone. An analogous dimerisation of ββ-dimethylacraldehyde (3-methylbut-2-enal) under basic conditions, *e.g.*, under the influence of sodamide, was observed by Fischer and Löwenberg [12] and was interpreted by them as a diene addition, but it was later suggested [13] that a Michael addition may be involved. We have now effected the dimerisation by lithium of ββ-dimethylacraldehyde (XII), which is accompanied by dehydration to the diene aldehyde (4-formyl-1 : 5 : 5-trimethyl*cyclo*hexa-1 : 3-diene), and under such conditions this reaction, like that of mesityl oxide, almost certainly proceeds by diene addition. As would be expected, pent-3-en-2-one also appears to undergo lithium-catalysed dimerisation, but the products in this case proved difficult to separate and purify and, as none could be obtained crystalline, they were not further examined. It is interesting that if "mixed" additions of this type could be effected, they would provide a new route, which could conceivably have biosynthetic significance, to monocyclic terpenes; thus ββ-dimethylacraldehyde with the enolate (XIIIa) of pent-3-en-2-one might yield the hydroxy-derivative shown and thence dehydro*cyclo*citral (XIV).

Experimental

Analytical data were determined in the organic microanalytical (Mr. F. H. Oliver and staff) and spectroanalytical (Mr. R. L. Erskine and Mrs. A. I. Boston) laboratories of this Department. Some of the infrared spectroscopic data were obtained in the laboratories of the British Rubber Producers' Research Association, by courtesy of Dr. G. Gee, F.R.S. Intensities of infrared absorption bands are indicated qualitatively by the symbols vs (very strong), s (strong), m (medium), and w (weak).

Dimerisation of Mesityl Oxide.—(*a*) Mesityl oxide (15 g.) was added to a stirred suspension of finely cut lithium (14 g.) in dry ether under nitrogen. The lithium rapidly assumed a bright, metallic appearance and a vigorous reaction commenced within about 10 min. More mesityl oxide (85 g.) was then added at such a rate that the ether continued to reflux gently. After a

[11] Pearson and Greer, *J. Amer. Chem. Soc.*, 1955, **77**, 1294, 6649.
[12] Fischer and Löwenberg, *Annalen*, 1932, **494**, 263; Fischer and Hultszch, *Ber.*, 1935, **68**, 1726; cf. Braude and Evans, *J.*, 1955, 3334.
[13] Jones and Koch, *J.*, 1942, 393.

further 1 hour's stirring, unchanged lithium (8 g.) was filtered off and 10% aqueous ammonium chloride (600 g.) was added. The ether layer was separated, dried (Na_2SO_4), and fractionated, giving some unchanged mesityl oxide (9 g.), a range of fractions (total 60 g.), b. p.s 60—90°/0·2 mm., and a high-boiling residue (16 g.). The intermediate fractions, when kept at 0° for several days, deposited crystals which were filtered off and recrystallised from pentane, giving 2-*acetyl*-1 : 3 : 3 : 5-*tetramethyl*cyclo*hex*-5-*en*-1-*ol* (II) (4 g.) as needles, m. p. 73° [Found: C, 73·1; H, 10·2%; *M* (in camphor), 198. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·3%; *M*, 196]. The m. p. was undepressed on admixture with the product, m. p. 74°, obtained by Braude and Coles.[1] Ultraviolet light absorption: $\lambda_{max.}$ 2550 Å (ε 40) and 2900 Å (ε 30 in EtOH). Infrared absorption: (i) As paraffin mull, $\nu_{max.}$ 3450 (m, hydrogen-bonded O–H stretching), 1700 (vs, C=O stretching), 1158 (s, C–O stretching), 829 and 808 cm.$^{-1}$ (m, >C=CH– bending); (ii) in CCl_4 (LiF prism), $\nu_{max.}$ 3578 (w, free O–H stretching) and 3475 cm.$^{-1}$ (m, hydrogen-bonded O–H stretching). With methylmagnesium iodide in ether, the dimer evolved methane corresponding to 1·03% (2·02 atoms) of "active" hydrogen. Microhydrogenation (acetic acid–platinic oxide) resulted in the uptake of 1·04 mols. of hydrogen. No 2 : 4-dinitrophenylhydrazone was formed on treatment with Brady's reagent, even after 2 days at room temperature. The dimer readily reacted with bromine in chloroform, but no solid products could be isolated.

(*b*) Finely cut lithium (3·5 g.) was added to a stirred solution of mesityl oxide (100 g.) in ether (500 ml.) under nitrogen. After about 10 min., a vigorous, exothermic reaction occurred. When this had subsided, the mixture was heated under reflux for 3 hr. and then worked up as above. A somewhat higher yield of solid dimer (10·7 g.), m. p. 73°, together with a similar mixture of liquid products was obtained.

Catalytic Hydrogenation of the Dimer.—(*a*) The dimer (1·0 g.) in ethyl acetate (30 ml.) was shaken with platinic oxide (50 mg.) in hydrogen. The uptake ceased when 124 ml. at 17°/760 mm. (Calc. for 1 mol., 123 ml.) had been absorbed. Removal of the catalyst and solvent gave 2-*acetyl*-1 : 3 : 3 : 5-*tetramethyl*cyclo*hexan*-1-*ol* (III) which crystallised from aqueous methanol in needles (0·6 g.), m. p. 76°, depressed to 67° on admixture with the starting material (Found: C, 72·8; H, 11·2. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%). Infrared light absorption (in CCl_4): $\nu_{max.}$ 3475 (m, O–H stretching), 1700 (vs, C=O stretching), 1458 (s), 1404 (s), 1373 (s), 1360 (s), 1335 (s), 1196 (s), and 1147 (s) cm.$^{-1}$. An attempted dehydration of the hydroxyketone (III) by iodine at 80°/10 mm. gave, after distillation, mainly unchanged starting material.

(*b*) The dimer (2·0 g.) in acetic acid (20 ml.) was shaken with platinic oxide in hydrogen. The uptake ceased after 6 hr. when 482 ml. at 18°/754 mm. (Calc. for 2 mol., 496 ml.) had been absorbed. The catalyst was filtered off and the solution was diluted with water (80 ml.) and extracted with ether. The ether extract was washed with aqueous sodium hydrogen carbonate, dried (K_2CO_3), and evaporated, giving 1-*acetyl*-2 : 2 : 4 : 6-*tetramethyl*cyclo*hexane* (IV) (1·4 g.) b. p. 94—96°/13 mm., n_D^{22} 1·4559 [Found: C, 78·8; H, 12·1%; *M* (in camphor), 176. $C_{12}H_{22}O$ requires C, 79·1; H, 12·2%; *M*, 182]. Infrared absorption (in CCl_4): $\nu_{max.}$ 1711 (vs, C=O stretching), 1449 (s), 1417 (m), 1380—1340 (s), 1230 (s), 1197 (s), and 1154 (s) cm.$^{-1}$. With methylmagnesium iodide in anisole, the ketone evolved methane corresponding to 0·55% (1·00 atom) of "active" hydrogen. Under similar conditions, the following results were obtained with other ketones: *cyclo*pentanone, 0·15; *cyclo*heptanone, 0·53; *iso*phorone, 0·28; 1-acetyl*cyclo*hexene, 0·31.

Dehydration of the Dimer.—(*a*) An intimate mixture of the dimer (0·77 g.) and anhydrous oxalic acid (1·54 g.) was heated for 2 hr. on the steam-bath and then extracted with ether. The ether solution was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled, giving a mixture [of 1-acetyl-2 : 4 : 6 : 6-tetramethyl*cyclo*hexa-1 : 3-diene (V) and 4-acetyl-1 : 5 : 5-trimethyl-3-methylene*cyclo*hexene (VI)], b. p. 98°/12 mm., n_D^{25} 1·4892 (Found: C, 80·3; H, 10·2. Calc. for $C_{12}H_{18}O$: C, 80·8; H, 10·2%). Ultraviolet light absorption in EtOH: Max. at 2360 (ε 4000), 2800 (ε 2000), and 3020 Å (ε 1000). Taking ε at 2360 Å as 9000 for pure (VI) (see below), this corresponds to a mixture of about 55% of (V) and 45% of (VI).

(*b*) The dimer (2·0 g.) and a trace of iodine were heated at 0·2 mm. As soon as the dimer had melted, a vigorous reaction took place and the mixture was distilled at *ca.* 75°. The product was dissolved in ether, washed with aqueous sodium thiosulphate, and dried (Na_2SO_4). Distillation gave 4-*acetyl*-1 : 5 : 5-*trimethyl*-3-*methylene*cyclo*hexene* (VI) (1·2 g.), b. p. 104°/15 mm., n_D^{17} 1·4942, $\lambda_{max.}$ 2360 Å (ε 9000 in EtOH) (Found: C, 80·3; H, 10·2%).

4-1′-*Hydroxyethyl*-1 : 5 : 5-*trimethyl*-3-*methylene*cyclo*hexene* (VII).—The dimer (0·5 g.) in ether (20 ml.) was treated with lithium aluminium hydride (1·1 g.) in ether (20 ml.) at room

temp. After 3 hr., saturated aqueous ammonium chloride (15 ml.) was added, the precipitate was filtered off and washed with ether, and the combined ether solution was dried (Na_2SO_4) and distilled, giving the *alcohol*, b. p. 76°/15 mm., n_D^{25} 1·4770, $\lambda_{max.}$ 2360 Å (ε 8000 in EtOH) (Found: C, 79·7; H, 11·2. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%). Infrared absorption (liquid film): $\nu_{max.}$ 3380 (s, hydrogen-bonded O–H stretching), 1647 (m, C=C stretching), 882 (s, >C=CH_2), 828 (m), and 792 (m, >C=CH–) cm.$^{-1}$.

2-1′-*Hydroxyethyl*-1 : 3 : 3 : 5-*tetramethyl*cyclo*hexanol* (VIII) (with D. Hughes).—2-Acetyl-1 : 3 : 3 : 5-tetramethyl*cyclo*hexan-1-ol (0·5 g.) was reduced with lithium aluminium hydride (1·1 g.) in ether at room temperature. After 3 hr., saturated aqueous ammonium chloride (15 ml.) was added and the ether layer was separated, washed with N-sulphuric acid and water, dried (Na_2SO_4), and evaporated, giving the *diol* (0·47 g.), m. p. 101—102°, raised to 104° by crystallisation from light petroleum (b. p. 60—80°) (Found: C, 71·9; H, 12·2. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·1%).

2 : 3 : 4 : 6-*Tetramethylacetophenone* (XI).—(*a*) The dimer (0·80 g.), tetrachloro-1 : 2-benzoquinone (5·0 g.), and dry benzene (6 ml.) were heated under reflux for 20 hr. Light petroleum (30 ml.; b. p. 40—60°) was then added and the mixture was kept overnight at room temperature and filtered. The solution was concentrated to about 10 ml. and chromatographed on alumina, with benzene as eluant. Distillation of the eluate gave 2 : 3 : 4 : 6-tetramethylacetophenone (0·42 g., 59%), n_D^{22} 1·5256, $\lambda_{max.}$ 2150 Å (ε 10,500), $\lambda_{infl.}$ 2450 (ε 2000) and 2780 Å (ε 800 in EtOH). The infrared spectrum was indistinguishable from that of the authentic specimen described below. Oxidation of the ketone (0·23 g.) with potassium hypochlorite followed by hydrolysis, as below, gave unchanged material (0·16 g.) and 2 : 3 : 4 : 6-tetramethylbenzoic acid (0·03 g., 15% or 43% on unrecovered ketone), m. p. and mixed m. p. 165°.

(*b*) Acetic anhydride (14 g.) was added slowly to a stirred mixture of *iso*durene (15 g.; b. p. 84—87°/17 mm., n_D^{23} 1·5112, prepared [14] from mesitylene), carbon disulphide (45 ml.), and freshly ground aluminium chloride (33 g.). After 30 min. at 80° the mixture was added to excess of ice, the carbon disulphide was allowed to evaporate, and the residue was extracted with ether. The ether extract was washed successively with water, 2N-sodium hydroxide, and water, dried (Na_2SO_4), and distilled, giving 2 : 3 : 4 : 6-tetramethylacetophenone (12 g., 61%), b. p. 135—137°/16 mm. After redistillation, it had b. p. 74°/0·3 mm., n_D^{21} 1·5248, $\lambda_{max.}$ 2160 Å (ε 10,500), $\lambda_{infl.}$ 2450 (ε 2000) and 2780 Å (ε 800) in EtOH (Found: C, 81·7; H, 9·2. Calc. for $C_{12}H_{16}O$: C, 81·8; H, 9·15%) (Smith and Guss [15] give b. p. 135—137°/16 mm.). Infrared absorption (liquid film): $\nu_{max.}$ 3360 (w, C=O stretching overtone), 2915 (s, C–H stretching), 1731 (vs, C=O stretching), 1604 (w), 1565 (w), 1447 (m), 1418 (m), 1400 (m), 1379 (m), 1350 (s), 1293 (m), 1255 (s), 1141 (s), 955 (m), 863 (m), and 742 (w) cm.$^{-1}$.

Unchanged ketone was recovered after refluxing with 2 : 4-dinitrophenylhydrazine and hydrochloric acid in aqueous ethanol for 2 hr. (cf. ref. 11) and with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol for 6 hr. An unstable oxime, m. p. 148° (no analytical data), was reported by Claus and Foecking.[16]

The ketone (5 g.) was added, with vigorous stirring, to aqueous potassium hypochlorite (9 g.) in water (70 ml.) at 55°. After overnight stirring, the excess of hypochlorite was destroyed by sodium hydrogen sulphite, and the mixture was extracted with ether. The solvent was removed and the residue was refluxed overnight with 2N-sodium hydroxide (150 ml.). The unchanged ketone (3·2 g.) was separated and the aqueous layer was acidified with hydrochloric acid. The precipitate was filtered off and extracted with ether. Evaporation and crystallisation from light petroleum (b. p. 60—80°) gave 2 : 3 : 4 : 6-tetramethylbenzoic acid [17] as prisms (0·8 g., 16% or 44% on unrecovered ketone), m. p. 165°.

Dimerisation of 3-*Methylbut-2-enal*.—The aldehyde (1·8 g.) in ether (25 ml.) was stirred overnight with finely divided lithium (0·07 g.) under nitrogen. Saturated aqueous ammonium chloride was added, the two layers were separated, and the aqueous layer was acidified and extracted with ether. The combined ether solution was dried (Na_2SO_4) and distilled, giving 4-formyl-1 : 5 : 5-trimethyl*cyclo*hexa-1 : 3-diene (0·8 g.), b. p. 80°/20 mm.; n_D^{20} 1·5000. This furnished a 2 : 4-*dinitrophenylhydrazone* which after chromatography on alumina in benzene–ethanol and crystallisation from ethyl acetate–light petroleum (b. p. 80—100°) had m. p. 200—201°, $\lambda_{max.}$ 4030 Å (ε 30,000 in $CHCl_3$) (Found: C, 58·4; H, 5·6; N, 16·8. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 17·0%).

[14] *Org. Synth.*, 1931, **11**, 24, 66.
[15] Smith and Guss, *J. Amer. Chem. Soc.*, 1937, **59**, 804.
[16] Claus and Foecking, *Ber.*, 1887, **20**, 3097.
[17] Gattermann, *Ber.*, 1899, **32**, 1116.

1-*Methyl*-3-*methylene*cyclo*hexene* (with Dr. O. H. WHEELER).—3-Methyl*cyclo*hex-2-enone [18] (8 g.) in ether (100 ml.) was added to methylmagnesium bromide (from methyl bromide, 6·5 ml., and magnesium, 2·4 g.) in ether (100 ml.) at 0°. After 1 hr. at room temperature, aqueous ammonium chloride was added and the ether layer was separated, dried, and distilled, giving 1 : 3-*dimethylcyclohex*-2-*enol* (9·2 g., 100%), b. p. 25—26°/1 mm., n_D^{19} 1·4764 (Found: C, 77·0; H, 11·0. $C_8H_{14}O$ requires C, 76·1; H, 11·2%).

The alcohol (4·2 g.) in dry pyridine (10 ml.) was treated with phosphorus oxychloride (8 ml.) in dry pyridine (20 ml.) with cooling. After the mixture had attained room temperature, it was heated on the steam-bath for 30 min. and then poured on excess of ice. The resulting mixture was extracted with *n*-pentane, and the extract was washed with 2N-hydrochloric acid and water, dried (Na_2SO_4), and distilled, giving 1-*methyl*-3-*methylene*cyclo*hexene* (2·3 g., 62%), b. p. 135—136°, n_D^{25} 1·4732, $\lambda_{max.}$ 2280 (ε 9500 in EtOH) (Found: C, 88·5; H, 11·4. C_8H_{12} requires C, 88·8; H, 11·2%). Haworth [19] gives b. p. 135—136°, n_D^{20} 1·4856, for a diene which he obtained directly from the reaction of the ketone with methylmagnesium iodide and formulated as 1 : 3-dimethyl*cyclo*hexa-1 : 3-diene.

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DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, SOUTH KENSINGTON, LONDON, S.W.7. [*Received, March 24th*, 1956.]

[18] Smith and Rouault, *J. Amer. Chem. Soc.*, 1943, **65**, 631; Bowman, Ketterer, and Dinga, *J. Org. Chem.*, 1952, **17**, 563.
[19] Haworth, *J.*, 1913, **103**, 1242.

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783. *Calciferol and its Relatives. Part II.* An Alternative Synthesis of* trans-1-2′-cyclo*Hexylidene-ethylidene-2-methylene*cyclo*hexane.*†

By B. LYTHGOE, S. TRIPPETT, and J. C. WATKINS.

The secondary alcohol (IV) and the tertiary amine (V) have been prepared and their elimination reactions studied. 1 : 4-Elimination of water from the alcohol gives the diconjugated triene (VI), whereas 1 : 4-elimination of dimethylamine from the amine (V) gives the triconjugated triene (I) named in the title.

THE triconjugated triene, *trans*-1-2′-*cyclo*hexylidene-ethylidene-2-methylene*cyclo*hexane (I) is of interest because of the similarity of its unsaturated system to that present in calciferol. In Part I * two routes were described for the preparation of the triene, both of which made use of Wittig and Schöllkopf's olefin synthesis [1] to introduce one of the double bonds. In the present paper we describe an alternative synthesis in which the double bonds are introduced solely by classical ionic elimination reactions.

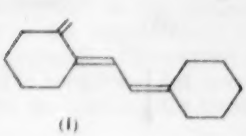
Formulæ (II)—(V) represent intermediates which might, in theory, be converted into the desired triene by elimination of appropriate oxygen and nitrogen functions. For each, however, alternative elimination pathways are open, which may be preferred because of the high energy of double bonds semicyclic to a *cyclo*hexane ring. Thus the readily accessible tertiary alcohol (II) has been shown [2] to lose water, giving not the triene (I), but an isomer in which the newly formed double bond is cyclic. Milas and Alderson [3] studied a simpler analogue of the amino-alcohol (III), and in the light of their results it is very probable that successive (indirect) elimination of water and dimethylamine would yield the desired triene (I). However, the preparation of this amino-alcohol by a Grignard reaction is apparently excluded by the allylic rearrangement which is known to take place when Grignard reagents derived from γ-substituted primary allyl halides react with

* Part I, *J.*, 1955, 4016.
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

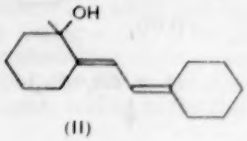
[1] Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.
[2] Dimroth, *Ber.*, 1938, **71**, 1346.
[3] Milas and Alderson, *J. Amer. Chem. Soc.*, 1939, **61**, 2534.

ketones;[4] no other simple route to the amino-alcohol (III) seems available. Accordingly we have studied the preparation and elimination reactions of the compounds (IV) and (V).

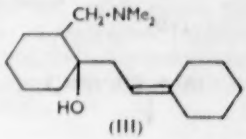
By using the abnormal Grignard reaction of allylic halides mentioned above, the alcohol (IV) was easily obtained. 1-Bromomethyl*cyclo*hexene formed a magnesium derivative which reacted with *cyclo*hexylideneacetaldehyde, giving the alcohol (IV) which, although no doubt a mixture of stereoisomers, formed a crystalline α-naphthylurethane, and its structure was confirmed by infrared bands at 888 (semicyclic methylene group) and 848 cm.$^{-1}$ (semicyclic trisubstituted double bond).



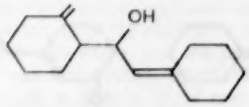
(I)



(II)



(III)



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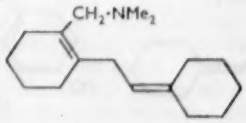
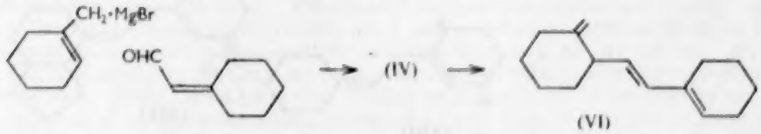


(V)

Two paths are theoretically open for its dehydration: 1 : 2-elimination, leading to the desired triene (I), and 1 : 4-elimination across the semicyclic trisubstituted double bond, leading to the diconjugated triene (VI). Dehydration took place readily in the presence of phosphoric oxide in light petroleum, the product consisting almost exclusively of the triene (VI), which showed the expected dienoid light adsorption at 234 mμ and infrared bands at 888 (semicyclic methylene group) and 967 cm.$^{-1}$ (*trans*-CH:CH). This preferential 1 : 4-elimination was not unexpected. The reaction probably follows



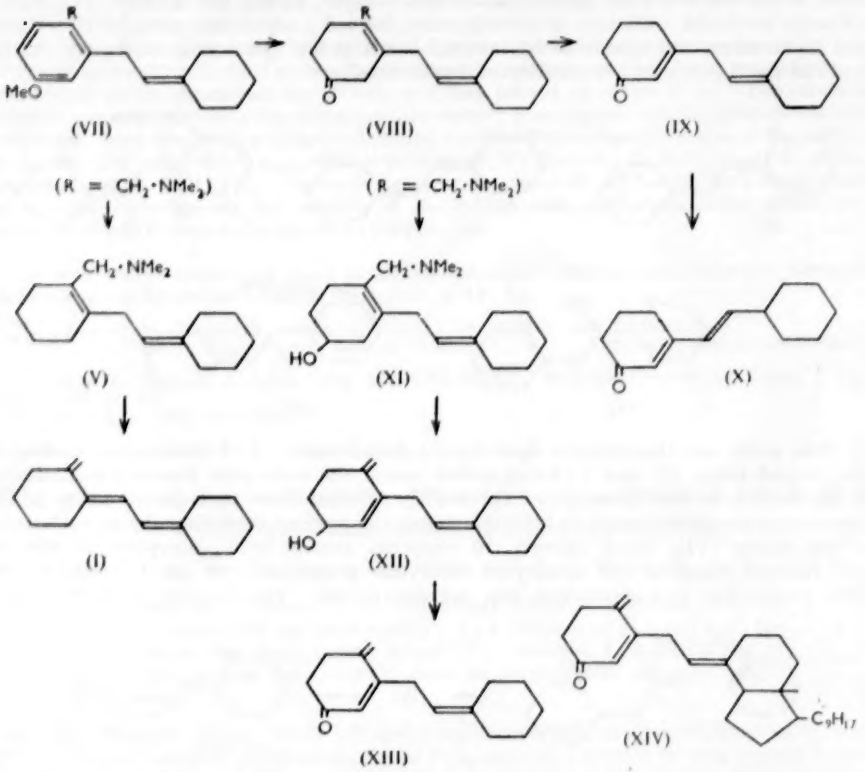
(VI)

a mechanism approximating to the E_1 type and subject to the generalised Saytzeff rule. One of the newly formed double bonds is purely acyclic, the other cyclic; both have less energy than the semicyclic trisubstituted double bonds present in (I). Thus the only factor favouring the 1 : 2-elimination reaction leading to the desired compound (I) is the triconjugation of the latter's triene system, but this factor will be of little significance because of the unfavourable *s-cis*-configuration of the semicyclic methylene group in relation to the other two double bonds. It seemed possible that 1 : 2-elimination from a structure of type (IV) might be promoted by altering the reaction mechanism, and with this aim we attempted to convert the alcohol (IV) into the bromide from which other suitable derivatives might be obtained. However, treatment with phosphorus tribromide caused anionotropic rearrangement to the corresponding tertiary bromide, and this approach was not further pursued.

Compounds of type (V) contain a dimethylaminomethyl*cyclo*hexene system, which we proposed to create by partial reduction of a suitable benzylamine. The route was first explored in model experiments. *m*-Methoxyphenylmagnesium bromide and *cyclo*hexylidene-ethyl bromide gave m-2′-*cyclo*hexylidene-ethylanisole (VII; R = H). Reduction with sodium and alcohol in liquid ammonia, followed by mild acid hydrolysis, gave 3-2′-*cyclo*hexylidene-ethyl*cyclo*hex-3-enone (VIII; R = H), whose structure was established

[4] Roberts and Young, *J. Amer. Chem. Soc.*, 1945, **67**, 148; 1946, **68**, 1472.

by lack of selective light absorption above 220 mμ and by stepwise isomerisation by acid, first to the unsaturated ketone (IX), and thence to the conjugated dienone (X). These displayed the expected light absorption maxima at 235 and 281 mμ respectively and were both characterised as semicarbazones.



By extension of the method, 2-bromo-4-methoxy-*NN*-dimethylbenzylamine was converted into its magnesium derivative, which with *cyclo*hexylidene-ethyl bromide gave the amine (VII; R = CH_2·NMe_2). During reduction of this with sodium and alcohol in liquid ammonia some over-reduction, accompanied by loss of the methoxyl group, took place, as previously observed [5] in parallel cases. After mild acid hydrolysis the product was reduced with lithium aluminium hydride to convert the ketone (VIII; R = CH_2·NMe_2) into the alcohol (XI), and the mixture so obtained was separated by chromatography on alumina into hydroxylic and non-hydroxylic fractions. The latter contained 2-dimethylaminomethyl-1-2′-*cyclo*hexylidene-ethyl*cyclo*hexene (V), originating in the loss of methoxyl function mentioned above; it was isolated as its crystalline methiodide which showed no selective light absorption above 220 mμ. Thermal decomposition of the corresponding quaternary hydroxide gave the desired triene (I), $\lambda_{max.}$ 270 mμ (ε 21,200); material purified by recrystallisation as described in Part I has $\lambda_{max.}$ 269·5 mμ (ε 22,700). The infrared absorption spectra of the two samples were identical. The overall yield of the triene (I) was very low, and for preparative purposes the present route is much inferior to those already described.

The alcohol (XI) present in the hydroxylic fraction from the chromatogram could not

[5] Birch, *J.*, **1946**, 593; **1947**, 1642.

be obtained crystalline either as such or as a derivative. The crude material was converted into the methiodide and thence into the quaternary hydroxide, which was decomposed by heat, giving a mixture of two materials showing light absorption at 234 and near 273 mμ severally. The minor component, which was responsible for the absorption near 273 mμ, may well have been the desired 5-hydroxy-derivative of (I), but we were unable to purify it. The component responsible for the light absorption at 234 mμ was identified as the diconjugated trienol (XII) as follows. Manganese dioxide did not attack the crude alcohol (XI), but oxidised the product from its Hofmann degradation, causing disappearance of the selective light absorption at 234 mμ and giving the conjugated dienone (XIII), characterised as the semicarbazone. The latter had $\lambda_{max.}$ 293 mμ, which agrees with that of the semicarbazone of the analogue (XIV), the product of Oppenauer oxidation of calciferol.[6] The contrast in the elimination of the amine (V) and its hydroxy-derivative (XI) is surprising, but may possibly be due to the allylic disposition of the hydroxyl group in stabilising the transition state leading to the alcohol (XII).

Experimental

1-Hydroxymethylcyclohexene.—1-Cyanocyclohexene[7] (57 g.), 95% alcohol (100 c.c.), and concentrated sulphuric acid (32 c.c.) were heated together under reflux for 72 hr., the cooled mixture was poured into water, and the product extracted with ether. The washed and dried ethereal solution was evaporated, distillation of the residual oil giving ethyl *cyclo*hex-1-enecarboxylate (57 g.), b. p. 104—111°/25 mm. This was added dropwise to a stirred suspension of lithium aluminium hydride (10·5 g.) in ether (300 c.c.) so that the ether refluxed gently, and stirring was then continued for ½ hr. Excess of hydride was decomposed by water, the cooled mixture poured into 10% hydrochloric acid (1·2 l.) with stirring, and the product isolated with ether. Distillation under reduced pressure gave 1-hydroxymethyl*cyclo*hexene (34 g.), b. p. 96°/18 mm. The phenylurethane[8] had m. p. 96° (Found: C, 72·7; H, 7·3; N, 6·15. Calc. for $C_{14}H_{17}O_2N$: C, 72·7; H, 7·4; N, 6·1%).

1-1′-Hydroxy-2′-cyclohexylidene-ethyl-2-methylenecyclohexane (IV).—1-Hydroxymethyl-*cyclo*hexene (10 g.) in light petroleum (25 c.c., b. p. 40—60°) was cooled to −12°, stirred, and treated dropwise with phosphorus tribromide (9 g.) in light petroleum (8 c.c.). The mixture was kept at −12° for 1 hr., then at room temperature for 24 hr., after which it was poured into ice-water and extracted with ether. The ethereal solution was washed with ice-cold aqueous sodium hydrogen carbonate and with water, dried, and evaporated. Distillation of the residue under reduced pressure gave 1-bromomethyl*cyclo*hexene (9 g.), b. p. 86—87°/17 mm. A portion (6·9 g.) was converted into the Grignard reagent by reaction with powdered magnesium (7 g.) in ether (65 c.c.). Ether (32 c.c.) was then distilled off and replaced by benzene (32 c.c.), after which a solution of *cyclo*hexylideneacetaldehyde (1·7 g.) in ether (5 c.c.) and benzene (5 c.c.) was added slowly with stirring. The mixture was stirred and heated under reflux for ½ hr., then cooled and poured into 10% aqueous ammonium chloride (200 c.c.). The product was isolated with ether in the usual manner and its solution in light petroleum (200 c.c.; b. p. 40—60°) chromatographed on neutral aluminium oxide (200 g.; deactivated by addition of 10 g. of water). The column was washed with more light petroleum (400 c.c.) and with benzene–light petroleum (400 c.c.; 2 : 1), and the filtrates were discarded; elution with benzene (600 c.c.) then gave *1-1′-hydroxy-2′-cyclohexylidene-ethyl-2-methylenecyclohexane* (1·67 g.) as a colourless oil (Found: C, 82·0; H, 11·2. $C_{15}H_{24}O$ requires C, 81·8; H, 11·0%). It showed no selective light absorption above 220 mμ. The *α-naphthylurethane* separated from light petroleum as rosettes of needles, m. p. 98—100° (Found: C, 80·0; H, 8·2; N, 3·75. $C_{26}H_{31}O_2N$ requires C, 80·2; H, 8·0; N, 3·6%).

Dehydration. A solution of the above alcohol (46 mg.) in light petroleum (1 c.c.; b. p. 60—80°) containing phosphoric oxide (30 mg.) was warmed under reflux for 2 hr., then kept at room temperature for 24 hr., and filtered. Evaporation gave an oil with $\lambda_{max.}$ 234 mμ (ε 16,500 in EtOH) and an inflection at 273 mμ (ε 3000). Its infrared absorption spectrum showed no band near 3300 cm.$^{-1}$ (absence of OH group) but showed *inter al.* bands at 1650 (m), 888 (vs) and 967 (s) cm.$^{-1}$.

m-2′-cyclohexylidene-ethylanisole (VII; R = H).—To a solution of the magnesium

[6] Trippett, *J.*, 1955, 370.
[7] Bhattacharyya, *J. Indian Chem. Soc.*, 1945, **22**, 85.
[8] Kohler, Tishler, Potter, and Thompson, *J. Amer. Chem. Soc.*, 1939, **61**, 1057.

derivative prepared from *m*-bromoanisole (25·4 g.) and magnesium (3·1 g.) in ether (200 c.c.) a solution of 2-*cyclo*hexylidene-ethyl bromide (21·5 g.) in ether (100 c.c.) was added slowly with stirring, and the mixture was heated under reflux for 2 hr., then cooled and decomposed with water. The product was isolated with ether and distilled under reduced pressure, giving m-2′-cyclo*hexylidene-ethylanisole*, b. p. 114—118°/0·4 mm. (Found : C, 83·5; H, 9·5. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%).

Reduction of m-2′-cyclo*Hexylidene-ethylanisole with Sodium in Liquid Ammonia.*—A solution of the above compound (7·8 g.) in alcohol (40 c.c.) and ether (50 c.c.) was added to liquid ammonia (700 c.c.) with stirring, which was continued for 4 hr. during the portionwise addition of sodium (11 g.). From the final colourless solution ammonia was allowed to evaporate, then water (300 c.c.) was added cautiously and the crude product (7·8 g.) was isolated with ether. Its ultraviolet absorption showed the presence of about 5% of unreduced material. A portion (5·7 g.) dissolved in alcohol (200 c.c.) containing 3N-sulphuric acid (14·5 c.c.) was kept at room temperature for 15 min., then diluted with water and extracted with ether. The concentrated ether extract (40 c.c.) was shaken twice with saturated aqueous sodium hydrogen sulphite (50 c.c.) for 15 hr. and the bisulphite compound separated by centrifugation. It was decomposed with N-sodium carbonate, and the product was isolated with ether and distilled under reduced pressure, giving 3-2′-cyclo*hexylidene-ethyl*cyclo*hex-3-enone* (2 g.), b. p. 104—106°/0·2 mm. (Found : C, 81·9; H, 10·1. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%). It showed no specific absorption above 220 mμ. Attempts to characterise it as the semicarbazone caused partial conversion into the semicarbazone of the αβ-unsaturated isomer, as shown by the light absorption of the product.

Isomerisation.—The unconjugated ketone (500 mg.), alcohol (80 c.c.), and 3N-sulphuric acid (20 c.c.) were boiled together under nitrogen for 1 hr. From the cooled and diluted solution the product was extracted with ether, and the ethereal extract was shaken with saturated sodium hydrogen sulphite in order to free it from starting material. The ethereal solution was washed, dried, and evaporated, and the residue treated with a solution of semicarbazide acetate in aqueous alcohol. Recrystallisation of the product from alcohol gave 3-2′-cyclo*hexylidene-ethyl*cyclo*hex-2-enone semicarbazone*, m. p. 170—171° (Found : C, 68·6; H, 9·1; N, 16·0. $C_{15}H_{23}ON_3$ requires C, 68·9; H, 8·9; N, 16·1%). Light absorption in EtOH : max. at 268 mμ (ε 28,900). The ketone, obtained by treatment with pyruvic acid in aqueous acetic acid in the usual manner, showed $\lambda_{max.}$ 235 mμ (ε 12,500 in EtOH). A portion (110 mg.) in alcohol (40 c.c.) containing 3N-sulphuric acid (10 c.c.) was heated under reflux under nitrogen for 24 hr. The product, isolated in the usual way, was a colourless oil, b. p. 160° (bath-temp.)/0·2 mm., which had $\lambda_{max.}$ 281 mμ (ε 17,800 in EtOH). Reaction with semicarbazide gave 3-2′-cyclo*hexylvinyl*-cyclo*hex-2-enone semicarbazone* which formed leaflets (from alcohol), m. p. 203° (Found : C, 69·05; H, 8·8; N, 15·9. $C_{15}H_{23}ON_3$ requires C, 68·9; H, 8·9; N, 16·1%). It showed λ_{max} 298 mμ (ε 41,800 in EtOH).

2-*Bromo*-4-*methoxy*-NN-*dimethylbenzylamine.*—A stream of hydrogen chloride was passed through a vigorously stirred suspension of *m*-bromoanisole (72 g.) in 40% aqueous formaldehyde (60 g.) at 40° for 4 hr. The product was extracted with chloroform, and the extract washed, dried, and evaporated. Fractional distillation of the residue under reduced pressure gave 2-*bromo*-4-*methoxybenzyl chloride* (52 g.), b. p. 107°/1 mm. (Found : C, 41·1; H, 3·75. C_8H_8OClBr requires C, 40·8; H, 3·4%), and 5-*bromo*-2 : 4-*di*(*chloromethyl*)*anisole* (10 g.), b. p. 130—135°/1 mm., which separated from light petroleum (b. p. 40—60°) as needles, m. p. 79° (Found : C, 38·3; H, 3·5. $C_9H_9OCl_2Br$ requires C, 38·1; H, 3·2%).

The above monochloromethyl compound (21·4 g.) was heated under reflux for 1½ hr. with 25% aqueous dimethylamine (27 c.c.) and alcohol (180 c.c.). The alcohol was then removed and the mixture shaken with 3N-sulphuric acid and ether. The acid phase was made strongly alkaline with aqueous sodium hydroxide, and the product isolated with ether and distilled, giving 2-bromo-4-methoxy-*NN*-dimethylbenzylamine (13 g.), b. p. 88°/0·5 mm. The *picrate* separated from alcohol as yellow prisms, m. p. 135—138° (Found : C, 40·25; H, 3·8; N, 12·1. $C_{16}H_{17}O_8N_4Br$ requires C, 40·6; H, 3·6; N, 11·8%).

2-2′-cyclo*Hexylidene-ethyl*-4-*methoxy*-NN-*dimethylbenzylamine* (VII; R = CH_2·NMe_2).—To magnesium (5·9 g.) in ether (10 c.c.) ethyl bromide (1 g.) was added and, when vigorous reaction had set in, a nitrogen atmosphere was maintained above the stirred mixture during the gradual addition of a mixture of the above tertiary base (30 g.), ethyl bromide (12·4 g.), and ether (150 c.c.). When this was complete the stirred mixture was heated under reflux for 1 hr., a solution of 2-*cyclo*hexylidene-ethyl bromide (49 g.) in ether (50 c.c.) was added slowly, and stirring and heating were continued for a further 2 hr. The mixture was cooled and treated

with water (200 c.c.), the ether layer was washed and evaporated, and the residue extracted with 3N-sulphuric acid. The acid extract was made alkaline and the product isolated with ether and distilled, giving 2-2′-cyclo*hexylidene-ethyl*-4-*methoxy*-NN-*dimethylbenzylamine* (13 g.), b. p. 137—144°/0·3 mm. (Found: C, 78·1; H, 9·9; N, 5·9. $C_{18}H_{27}ON$ requires C, 79·1; H, 9·9; N, 5·9%). The methiodide formed plates (from alcohol–ether), m. p. 194° (decomp.).

Reduction of 2-2′-cyclo*Hexylidene-ethyl*-4-*methoxy*-NN-*dimethylbenzylamine with Sodium in Liquid Ammonia.*—A solution of the tertiary base (3·56 g.) in alcohol (14·5 c.c.) and ether (12 c.c.) was added to stirred liquid ammonia (150 c.c.), and sodium (5·5 g.) was added in small portions during 4 hr., after which stirring was continued for a further 4 hr. and the remaining blue colour finally discharged by adding alcohol (2·5 c.c.). When the ammonia had evaporated water (150 c.c.) was added to the stirred mixture, from which the crude product (3·44 g.) was isolated with ether. It was hydrolysed by keeping its solution in 0·28N-sulphuric acid at room temperature for ½ hr., and the product obtained by making the solution alkaline was isolated with ether. A solution of the hydrolysis product (3·25 g.) in ether (40 c.c.) was added slowly to a stirred suspension of lithium aluminium hydride (0·5 g.) in ether (10 c.c.), and the mixture was warmed under reflux for 1 hr. Excess of hydride was decomposed with saturated aqueous sodium sulphate, and the mixture was treated with anhydrous sodium sulphate and filtered, the solid residue being well washed with ether. Evaporation of the filtrate and washings gave a colourless oil (3·2 g.) which was dissolved in light petroleum (10 c.c.; b. p. 40—60°) and passed through neutral alumina (130 g.; deactivated by addition of 5% of water). The column was washed successively with light petroleum (500 c.c.; b. p. 40—60°), with light petroleum–benzene (1 : 1; 4 × 300 c.c.), with benzene (600 c.c.), and finally with 1 : 99 methanol–benzene (300 c.c.).

trans-1-2′-cyclo*Hexylidene-ethylidene*-2-*methylene*cyclo*hexane* (I). Evaporation of the first light petroleum–benzene eluate (300 c.c.) gave an oil (410 mg.) which on treatment with methyl iodide in benzene furnished 2-*dimethylaminomethyl*-1-2′-cyclo*hexylidene-ethyl*cyclo*hexene methiodide* as plates (from alcohol–ether), softening at 168°, resolidifying above 170°, and remelting at 230—255° (decomp.) (Found: C, 55·65; H, 8·5; N, 3·7. $C_{18}H_{32}NI$ requires C, 55·5; H, 8·3; N, 3·6%). It showed no specific light absorption above 220 mμ. A portion (36 mg.) was shaken in aqueous methanol (1 c.c.) with silver oxide (46·5 mg.) for ½ hr., then the filtered solution was evaporated and the residue distilled at 110°/0·5 mm. The distillate consisted of *trans*-1-2′-*cyclo*hexylidene-ethylidene-2-methylene*cyclo*hexane and had $\lambda_{max.}$ 270 mμ (ε 21,200), $\lambda_{min.}$ 230 mμ (ε 5700). Its infrared absorption spectrum was identical with that of authentic material prepared as described in Part I.

3-2′-cyclo*Hexylidene-ethyl*-4-*methylene*cyclo*hex*-2-*enone* (XIII). Evaporation of the 1 : 99 methanol–benzene eluate from the chromatogram yielded an oil (1·25 g.) consisting of crude 4-dimethylaminomethyl-3-2′-*cyclo*hexylidene-ethyl*cyclo*hex-3-en-ol. A portion (343 mg.) was converted in the usual manner into the methiodide and thence into the quaternary hydroxide, which was distilled at 130—140°/0·5 mm., giving a colourless viscous oil (192 mg.) showing $\lambda_{max.}$ 234 and 274 mμ in EtOH. It was shaken in light petroleum (10 c.c.; b. p. 40—60°) with manganese dioxide [9] (2 g.) for ¾ hr., after which the solution was filtered and evaporated and the product distilled at 110—130° (bath-temp.)/0·5 mm. Treatment of the distillate with semicarbazide in aqueous alcohol gave 3-2′-cyclo*hexylidene-ethyl*-4-*methylene*cyclo*hex*-2-*enone semicarbazone* as needles (from alcohol), m. p. 203—204° (Found: C, 70·5; H, 8·2; N, 15·5. $C_{16}H_{25}ON_3$ requires C, 70·3; H, 8·5; N, 15·4%). Light absorption: max. at 293 mμ (ε 34,500 in $CHCl_3$).

One of us (J. C. W.) thanks the University of Western Australia for a Hackett Studentship.

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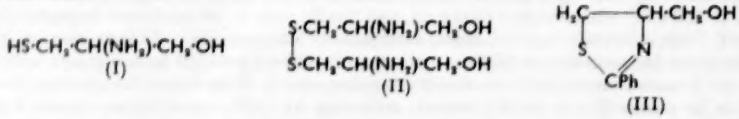
[9] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

784. *Synthesis of Cystinol.**

By J. C. Crawhall, D. F. Elliott, and K. C. Hooper.

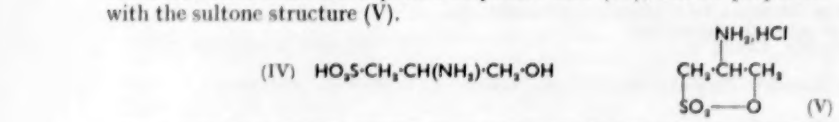
Cystinol (II) and some derivatives of cysteinol (I) have been prepared and their properties examined with a view to their use in the characterisation of *C*-terminal cysteine residues in proteins and peptides.

In connection with a study of the reduction of the *C*-terminal residues of peptides and proteins with metal hydrides [1] it was necessary to prepare 2-amino-3-hydroxypropane-1-thiol (cysteinol) (I) or its disulphide derivative (cystinol) (II).† Reduction of cysteine methyl ester with lithium aluminium hydride yielded a mixture containing some cysteinol, but the pure compound could not be isolated. A similar reduction of the thiazolidine derivative from cysteine methyl ester and benzaldehyde was also unsuccessful. The desired reduction took place when 4-alkoxycarbonyl-2-phenylthiazolines were treated with lithium aluminium hydride. The thiazoline alcohol (III) thereby obtained yielded on hydrolysis a solution giving a positive nitroprusside reaction and presumably containing cysteinol, but this substance could not be crystallised nor could crystalline derivatives be obtained. Mild oxidation of the solution, however, afforded cystinol as a crystalline dihydrochloride.



It was necessary to consider the conditions under which cysteinol or cystinol might be isolated from the mixture obtained when a peptide containing *C*-terminal cysteine had been reduced by a metal hydride and hydrolysed. In practice it is very difficult to avoid oxidation of thiol groups during hydrolysis and the product would certainly contain cystinol and, owing to the disulphide interchange reaction,[2] a mixed disulphide of cysteinol and cysteine might also be present. This complication might be overcome by conversion of the mixed disulphides into thiols by reduction, or into sulphonic acids by oxidation. Accordingly, the chromatographic properties of cysteinol and its derivative with *N*-ethylmaleimide [3] were examined in several solvent systems. *S*-Benzylcysteinol, a compound of possible value for the isolation of cysteinol from hydrolysates, was prepared from *S*-benzylcysteine methyl ester and isolated as the oxalate.

Oxidation of cysteinol hydrochloride with performic acid [4] yielded cysteic acid, whereas bromine water oxidation yielded variable results. In some experiments with bromine only cysteic acid was produced, but occasionally a neutral substance was obtained; this was prepared more easily by the action of bromine water on cystinol hydrochloride. Unlike an amino-alcohol, it was not attacked by periodate ions, and the absence of a disulphide grouping was demonstrated by a negative result with alkaline potassium cyanide–sodium nitroprusside solution. A potentiometric titration showed that a sulphonic acid grouping was not present; the titration curve was typical of an amine hydrochloride. The substance could not have been the expected sulphonic acid (IV), but its properties were consistent with the sultone structure (V).



* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

† In view of the trivial names adopted for amino-alcohols derived from naturally occurring amino-acids, it seems justifiable to name these two substances as cysteinol and cystinol, respectively.

[1] Crawhall and Elliott, *Biochem. J.*, 1955, **61**, 264.
[2] Ryle and Sanger, *ibid.*, 1955, **60**, 535.
[3] Hanes, Hird, and Isherwood, *Nature*, 1950, **166**, 288.
[4] Sanger, *Biochem. J.*, 1949, **44**, 126.

The R_F values of the various cysteinol derivatives, compared with the corresponding derivatives of cysteine, are given in the Table; these cysteinol derivatives all gave blue spots when their chromatograms were sprayed with the ninhydrin reagent used for detecting amino-acids.

Experimental

L-4-*Ethoxycarbonyl-2-phenylthiazoline.*—L-Cystine {$[\alpha]_D^{22.5}$ −177° (*c* 1·003 in N-HCl); 25 g.} was reduced with a slight excess of sodium in liquid ammonia, the excess of sodium was decomposed with ammonium chloride, and the ammonia evaporated. The product was suspended in ethanol (250 ml.), and a rapid stream of dry hydrogen chloride passed in until the solvent boiled. Ammonium chloride was removed by filtration, and the filtrate saturated with hydrogen chloride at 0°. After boiling under reflux for 30 min. the solvent was evaporated and the crystalline residue of L-cysteine ethyl ester hydrochloride recrystallised from ethanol–ether. The yield was 28 g. (72%), and the m. p. 120—121°.

	Solvent system no.					Solvent system no.			
	1	2	3	4		1	2	3	4
Cystinol	0·95	0·60	0·05	0·05	*N*-Ethylmaleimide derivative of:				
Sultone (IV)	0·56	0·34	0·18	0·14	Cysteinol	0·95	0·88	0·50	0·31
Cysteic acid	0·08	0·04	0·04	0·00	Cysteine	0·88	0·34	0·39	0·18
Cystine	0·3	0·04	0·03	0·00					

Solvent systems: 1, phenol–ammonia;[a] 2, *sec.*-butyl alcohol–ammonia;[b] 3, *sec.*-butyl alcohol–formic acid;[b] 4, *n*-butyl alcohol–acetic acid.[c]

[a] Consden, Gordon, and Martin, *Biochem. J.*, 1944, **38**, 224. [b] Hausmann, *J. Amer. Chem. Soc.*, 1952, **74**, 3181. [c] Fromageot, Jutisz, Meyer, and Penasse, *Biochem. Biophys. Acta*, 1950, **6**, 283.

The ester hydrochloride (37·5 g.) was dissolved in ethanol (100 ml.) by warming. Ethyl benzimidate[d] (30 g.) was then added and the mixture kept at room temperature for 1 hr. A mild exothermic reaction occurred after a few minutes and ammonium chloride was deposited. The L-4-*ethoxycarbonyl-2-phenylthiazoline* (38·2 g., 80·5%) remaining after filtration of the ammonium chloride and evaporation of the solvent had b. p. 162°/0·5 mm., $[\alpha]_D^{22.5}$ +14·6° (*c* 1·098 in EtOH) (Found: C, 61·5; H, 5·2; N, 5·7. $C_{12}H_{13}O_2NS$ requires C, 61·3; H, 5·5; N, 5·9%).

DL- *and* L-4-*Hydroxymethyl-2-phenylthiazoline.*—DL-4-Methoxycarbonyl-2-phenylthiazoline (Crawhall and Elliott;[e] 3·7 g.) was dissolved in anhydrous ether (50 ml.) and added to a sludge of lithium aluminium hydride (0·6 g.) in anhydrous ether (50 ml.) at such a rate as to maintain gentle boiling. The solution became bright yellow. After 10 min. water (5 ml.) was added, the solution was filtered, and the ethereal layer was washed with water until colourless, dried (Na_2SO_4), and evaporated. The residual *thiazoline alcohol* crystallised from light petroleum (b. p. 60—80°). The yield was 1·7 g. (53%) and the m. p. 75—76° (Found: C, 61·9; H, 5·4. $C_{10}H_{11}ONS$ requires C, 62·2; H, 5·7%).

In a similar way L-4-ethoxycarbonyl-2-phenylthiazoline (10 g.) gave L-4-*hydroxymethyl-2-phenylthiazoline* (4·6 g., 56%), m. p. 75—76° (Found: C, 62·4; H, 5·7; N, 7·2; S, 16·8. $C_{10}H_{11}ONS$ requires C, 62·2; H, 5·7; N, 7·2; S, 16·6%). The compound had no optical rotation in EtOH at 23·5° (*c* 0·545) but yielded an optically active sultone hydrochloride (see below).

DL-*Cystinol Dihydrochloride.*—DL-4-Hydroxymethyl-2-phenylthiazoline (1 g.) was refluxed in concentrated hydrochloric acid (20 ml.) for 6 hr. in a stream of nitrogen. The cooled solution was extracted with ether and then evaporated to dryness. Cysteinol hydrochloride remained as an oil which gave a positive reaction with sodium nitroprusside and with Hopkins reagent yielded a green precipitate which rapidly darkened with liberation of hydrogen sulphide. When an aliquot part was titrated in N-hydrochloric acid at 0° with 0·1N-iodine, 90% of the theoretical amount for one thiol group was consumed.

The crude hydrochloride (0·27 g.) was dissolved in water (10 ml.) and the solution made alkaline with ammonia. A small crystal of ferrous sulphate was added and a rapid stream of air passed through the solution until the mauve colour had disappeared (1·5 hr.). The solution was kept overnight, the precipitate of iron hydroxide was removed by centrifugation, and the solvent evaporated. The *dihydrochloride* was crystallised by dissolving it in hot concentrated

[d] Elliott, *Biochem. J.*, 1949, **44**, 429.
[e] Crawhall and Elliott, *J.*, 1951, 2071.

hydrochloric acid and adding alcohol. The yield was 0·2 g. (74%), and the m. p. 183° (Found: C, 25·2; H, 6·0; N, 9·8. $C_6H_{14}O_2N_2S_2Cl_2$ requires C, 25·3; H, 6·3; N, 9·8%). The compound did not react with sodium nitroprusside solution, but gave a positive thiol test when potassium cyanide was added to the mixture.

L- *and* DL-*2-Amino-1-hydroxypropane-3-sulphonic Sultone Hydrochloride.*—L-Cysteinol hydrochloride, obtained by hydrolysis of L-4-hydroxymethyl-2-phenylthiazoline (3 g.) in the usual way, was dissolved in water (10 ml.) and a slight excess of bromine water added. The solution was evaporated, leaving a white solid which was crystallised from aqueous acetic acid. The *L-sultone hydrochloride* (0·43 g.) had m. p. 164—166°, $[\alpha]_D^{28}$ −5·6° (*c* 1·25 in H_2O). It gave no reaction with sodium periodate solution, sodium hydrogen carbonate solution, or alkaline potassium cyanide–sodium nitroprusside solution (Found: C, 20·6; H, 5·0; N, 7·7. $C_3H_6O_3NSCl$ requires C, 20·8; H, 4·6; N, 8·1%).

In some instances, this oxidation could not be controlled and only cysteic acid was obtained. The latter was the sole product when performic acid was used for the oxidation of cysteinol. The cysteic acid produced in these oxidations was identified by analysis (Found: C, 21·5; H, 3·8. Calc. for $C_3H_7O_5NS$: C, 21·3; H, 4·1%) and by its infrared absorption spectrum, which was identified with that of an authentic sample.

In the preparation of DL-*sultone hydrochloride*, it was preferable to use DL-cystinol dihydrochloride. The dihydrochloride (0·15 g.) when dissolved in water (2 ml.) and oxidised with bromine water gave the DL-sultone hydrochloride (0·08 g.) which, crystallised from aqueous acetic acid, had m. p. 251—252° (decomp.). Difficulty was experienced in obtaining accurate analyses for this compound (Found: C, 19·9; H, 4·5; Cl, 18·2. Calc. for $C_3H_6O_3NSCl$: C, 20·8; H, 4·6; Cl, 20·4%), but its structure followed from its chemical properties which were identical with those of the L-sultone. On potentiometric titration in aqueous solution, the compound combined with one equivalent of alkali between pH 6 and pH 10. This is considered to be due to the conversion of the NH_3^+ group into the un-ionised form.

L-S-*Benzylcysteinol Oxalate.*—*S*-Benzylcysteine ethyl ester hydrochloride (10 g.) was treated with triethylamine (3·7 g.), and the free ester extracted into ether. Reduction was carried out with lithium aluminium hydride (2 g.) in the usual way. The crude product was an oil (2·6 g.) to which was added a saturated solution of oxalic acid in ethanol. L-S-*Benzylcysteinol oxalate* (2·65 g.) crystallised and after seven recrystallisations from ethanol had m. p. 181—183°, $[\alpha]_D^{19\cdot5}$ −61·2° (*c* 0·196 in MeOH) (Found: C, 54·6; H, 6·8; N, 5·8. $C_{22}H_{28}O_6N_2S_2$ requires C, 54·6; H, 6·6; N, 5·8%).

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785. *The Synthesis of (±)-Angustione and Related Compounds.**

By G. R. Ensor and W. Wilson.

4 : 4-Dimethyl- and 4 : 4 : 6-trimethyl-*cyclo*hexane-1 : 3-diones have been synthesised. Synthetic (±)-2-acetyl-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione is identical with (±)-angustione.

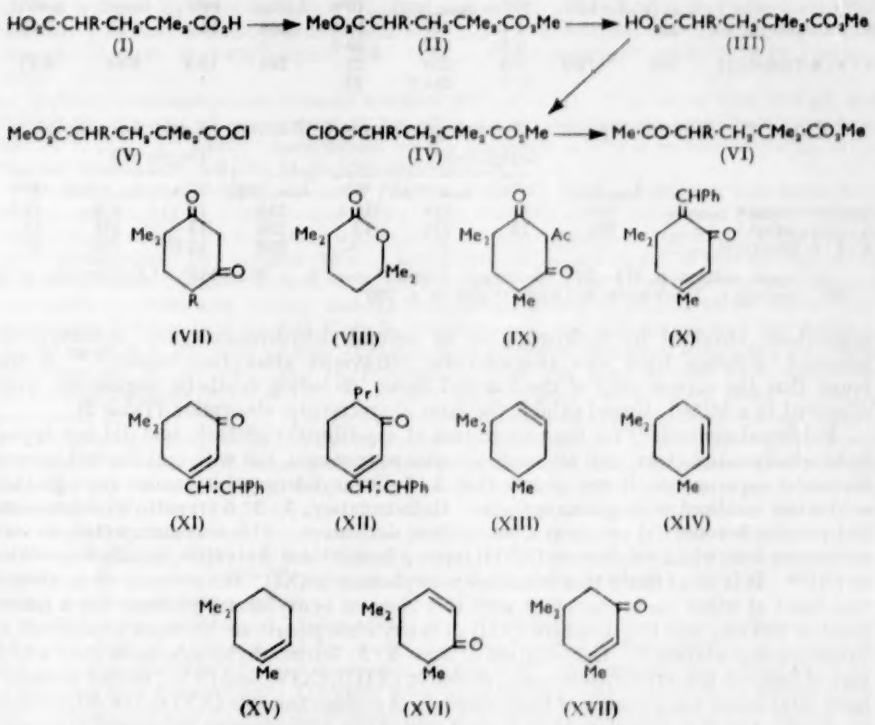
The *cyclo*hexane-1 : 3-dione derivatives (−)-angustione and dehydroangustione, isolated from *Backhousia angustifolia*, were investigated several years ago in Simonsen's laboratory.[1,2] The revised structure (IX) recently proposed by Birch [3] has now been confirmed by the total synthesis of (±)-angustione. Soon after the publication [4] of a preliminary account of this work, Chan and Hassall [5] independently described the synthesis of (±)-angustione by a different method.

In model experiments, dimethyl αα-dimethylglutarate (II; R = H) was selectively hydrolysed by alkali to the half-ester (III; R = H), the second methoxycarbonyl group

* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Gibson, Penfold, and Simonsen, *J.*, 1930, 1184.
[2] Cahn, Gibson, Penfold, and Simonsen, *J.*, 1931, 286.
[3] Birch, *J.*, 1951, 3026.
[4] Ensor and Wilson, *Chem. and Ind.*, 1955, 2860.
[5] Chan and Hassall, *J.*, 1955, 2860.

being sterically hindered. The corresponding ester chloride (IV; R = H) with dimethylcadmium afforded the oxo-ester (VI; R = H), which was cyclised by sodium methoxide (cf. ref. 6) to 4 : 4-dimethyl*cyclo*hexane-1 : 3-dione (VII; R = H) which had the expected physical characteristics (Table 1; cf. ref. 7). A by-product from the dimethylcadmium reaction was a crystalline lactone $C_9H_{16}O_2$; this is formulated as (VIII), which could arise by a simple sequence of reactions. Although ester acid chlorides of type (IV) often partially isomerise [8] to (V), the ester chlorides (IV; R = H and Me) obtained in the present work gave homogeneous *p*-bromoanilides, and it is therefore assumed that rearrangement



did not occur. Isomerisation would not invalidate the synthesis, as each member of a pair of isomeric ester chlorides would yield the same *cyclo*hexane-1 : 3-dione.

By a similar sequence of reactions, $\alpha\alpha\gamma$-trimethylglutaric acid (I; R = Me) was converted into (±)-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (VII; R = Me), which had the characteristic properties of a *cyclo*hexane-1 : 3-dione (cf. refs. 6, 7). The same dione was originally obtained in the early degradative studies on angustione.[2] A crystalline by-product was obtained from the reaction between dimethylcadmium and the ester chloride (IV; R = Me); this product was found to be 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (VII; R = Me). Presumably, dimethylcadmium cyclised some of the oxo-ester (VI; R = Me), for dimethylcadmium catalyses the condensation of benzaldehyde with acetophenone,[9] and ethylmagnesium bromide effects certain Claisen condensations.[10]

[6] Meek, Turnbull, and Wilson, *J.*, 1953, 811.
[7] *Idem*, *J.*, 1953, 2891.
[8] Cason, *J. Org. Chem.*, 1948, **13**, 227.
[9] Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518.
[10] Hauser, Swamer, and Adams, *Org. Reactions*, 1954, **8**, 137.

It is well established [11,12] that *cyclo*hexane-1 : 3-diones undergo *C*-acylation at $C_{(2)}$. Treatment of (±)-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione with acetic anhydride–sodium acetate gave the liquid 2-acetyl compound (IX) which was characterised as the crystalline imine and copper salt. These derivatives were identical with those reported for (±)-

TABLE 1. *Light absorption and* p*K's of* cyclo*hexane*-1 : 3-*diones.*

	Ethanol		50% Ethanol					pK_a in 50% ethanol	
						Isosbestic point		Spectroscopic	Electrometric
	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	pH	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	λ (mμ)	$10^3\varepsilon$		
4 : 4-Dimethyl ...	255	18·4	2·45	257	18·3	266	13	6·18	6·20
			9·55	282	26·9				
4 : 4 : 6-Trimethyl	257	18·9	1·9	258	21	268	15·4	6·44	6·37
			12·3	284·5	31				

TABLE 2. *Light absorption of* 2-*acetyl*cyclo*hexane*-1 : 3-*diones in acidified ethanol.*

	Acetyl-dione				Copper salt			
	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$
Unsubstituted [a]	233	15	272	11·5	233	15	272	13·5
5 : 5-Dimethyl [b]	234	12	274	12	234	12	274	12
4 : 4 : 6-Trimethyl	—	—	—	—	235	10·5	275	10

[a] Copper salt, m. p. 271—272° (decomp.); Smith [13] gives m. p. 263—265°. [b] Copper salt, m. p. 260° (decomp.); Dieckmann and Stein [11] give m. p. 260°.

angustione, obtained by hydrogenation of natural dehydroangustione. 2-Acetyl*cyclo*hexane-1 : 3-diones have two characteristic ultraviolet absorption bands; [3,12] it was found that the copper salts of the 2-acetyl-diones, including synthetic angustione, when dissolved in acidified ethanol exhibit the same characteristic absorption (Table 2).

Published methods [13] for the preparation of ααγ-trimethylglutaric acid did not appear to be wholly satisfactory, and alternative routes were sought, but with only limited success. In model experiments, it was shown that 2 : 6-dibenzylidene*cyclo*hexanone gave glutaric acid when oxidised with permanganate. Unfortunately, 3 : 3 : 5-trimethyl*cyclo*hexanone (dihydro*iso*phorone) did not form a benzylidene derivative. This was unexpected, in view of the ease with which *iso*phorone (XVII) forms a benzylidene derivative, usually formulated as (X). [14] It is more likely that benzylidene*iso*phorone is (XI); the presence of an absorption band at 323·5 mμ is consistent with this view, as benzylidenepiperitone has a similar band at 323 mμ, and the structure (XII) of benzylidenepiperitone has been established by oxidative degradation. [15] Dehydration of *trans*-3 : 3 : 5-trimethyl*cyclo*hexanol gave a mixture of isomeric trimethyl*cyclo*hexenes, probably (XIII), (XIV), and (XV); earlier workers [16] have established the presence of large amounts of *cyclo*geraniolene (XV) in the dehydration products; but it is now clear that at least one of the other isomers mentioned is present. Chromic acid oxidation of the trimethyl*cyclo*hexene mixture gave a mixture of trimethyl*cyclo*hexenones. Some *iso*phorone [XVII; derived from (XV)] was present in the mixture, as shown by the isolation of *iso*phorone 2 : 4-dinitrophenylhydrazone. Permanganate oxidation of the ketone mixture afforded useful amounts of ααγ-trimethylglutaric acid; this indicates the presence of the trimethyl*cyclo*hexenone (XVI), derived from (XIII), or of an isomeric ketone derived from (XIV).

EXPERIMENTAL

Ultraviolet absorption and pK_a measurements (Tables) were carried out as described previously. [6,7]

[11] Dieckmann and Stein, *Ber.*, 1904, **37**, 3370; Crossley and Renouf, *J.*, 1912, 1524; Rogers and Smith, *J.*, 1955, 341.
[13] Smith, *J.*, 1953, 803.
[13] Perkin and Smith, *J.*, 1903, 771; Hoch and Karrer, *Helv. Chim. Acta*, 1954, **37**, 397.
[14] Cornubert and Borrel, *Compt. rend.*, 1926, **183**, 296; *Bull. Soc. chim. France*, 1929, **45**, 1158.
[15] Earl and Read, *J.*, 1926, 2072; cf. Bardhan and Adhya, *J.*, 1956, 260.
[16] Knoevenagel, *Annalen*, 1897, **297**, 199; Wallach and Franke, *ibid.*, 1902, **324**, 114; Wallach and Schennert, *ibid.*, p. 102.

Dimethyl αα-Dimethylglutarate.—Camphoric anhydride (177 g.) was converted [17] into *iso*lauronolic acid (94 g.; m. p. 132—134°). Oxidation [18] with nitric acid then afforded crude αα-dimethylglutaric acid, which was converted into the dimethyl ester (52 g.; b. p. 99—107°/12 mm.; Blaise [19] gives b. p. 215—216°) by boiling methanol and sulphuric acid. The light-absorption properties of *iso*lauronolic acid ($\lambda_{max.}$ 229 mμ; ε 9000) are consistent with an αβ-unsaturated acid structure.

γ-Methoxycarbonyl-γ-methylvaleric Acid (III; R = H).—Dimethyl αα-dimethylglutarate (10 g.), absolute ethanol (50 c.c.), and N-ethanolic potassium hydroxide (56 c.c.) were stirred at 20° for 24 hr., alcohol distilled off at 15 mm., and water (50 c.c.) added. A small amount of oil was removed by ether-extraction; acidification of the aqueous layer and ether-extraction afforded *γ-methoxycarbonyl-γ-methylvaleric acid* (5·8 g.), b. p. 135—140°/12 mm., n_D^{19} 1·4382 (Found: C, 55·6; H, 7·9%; equiv., 176. $C_7H_{12}O_2{\cdot}CO_2H$ requires C, 55·2; H, 8·1%; equiv., 174).

γ-Methoxycarbonyl-γ-methylvaleroyl Chloride (IV; R = H).—The above acid (5·8 g.) and thionyl chloride (8·1 g.) were heated at 30—40° for 4 hr., yielding the chloride (5·5 g.), b. p. 68—71°/2 mm., n_D^{18} 1·4475, characterised by the formation of a p-*bromoanilide* (76%), m. p. 72—74° (Found: N, 4·2. $C_{14}H_{18}O_2NBr$ requires 4·3%).

Methyl 2 : 2-Dimethyl-5-oxohexanoate (VI; R = H).—A Grignard solution was made from methyl bromide (11·4 g.), magnesium (2·89 g.), and ether (60 c.c.). Anhydrous finely powdered cadmium chloride (11 g.) was added with stirring and stirring continued at 30° until the Gilman test was negative. Dry benzene (70 c.c.) was added, and about 20 c.c. of this distilled off to remove the ether. *γ*-Methoxycarbonyl-*γ*-methylvaleroyl chloride (8·5 g.) in dry benzene (20 c.c.) was added dropwise with cooling, and the reaction completed by stirring at 80° for 40 min. After decomposition with ice and dilute hydrochloric acid, the benzene solution was distilled, to give an oil, b. p. 98—103°/12 mm. Crystals were gradually deposited, trituration with light petroleum (b. p. 40—60°), and recrystallisation from the same solvent gave *ααδδ-tetramethyl-δ-valerolactone* (VIII) (0·9 g.), m. p. 80·5—81·5° (Found: C, 69·7; H, 10·45. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The lactone gave a negative iodoform reaction, did not form a 2 : 4-dinitrophenylhydrazone, and had no absorption bands between 220 and 310 mμ; it slowly dissolved in aqueous alkali and was regenerated on acidification, and with concentrated aqueous ammonia gave *5-hydroxy-2 : 2 : 5-trimethylhexanoamide*, m. p. 123—124° (from ethyl acetate) (Found: N, 7·7. $C_9H_{19}O_2N$ requires N, 8·1%). The light petroleum liquors were distilled, to give methyl 2 : 2-dimethyl-5-oxohexanoate (VI; R = H) (4 g.), b. p. 100—102°/12 mm., n_D^{20} 1·4371 (Found: C, 62·8; H, 9·4. $C_9H_{16}O_3$ requires C, 62·7; H, 9·8%) [2 : 4-*dinitrophenylhydrazone*, m. p. 100—100·5° (Found: N, 15·65. $C_{15}H_{20}O_6N_4$ requires N, 15·9%)]; this ester gave a positive iodoform reaction.

4 : 4-*Dimethyl*cyclo*hexane*-1 : 3-*dione* (VII; R = H).—Solvent-free sodium methoxide (from 2·1 g. of sodium) was suspended in dry ether (40 c.c.) and methyl 2 : 2-dimethyl-5-oxohexanoate (3·8 g.) in dry ether (30 c.c.) added slowly with stirring at 5°. The mixture was stirred for 16 hr. at 20°, then iced water added. The ether layer was removed; the aqueous layer was acidified with hydrochloric acid and extracted with ether (4 × 60 c.c.); recrystallisation of the extract from ethyl acetate gave the *dione* (1·4 g.), m. p. 103—105° (Found: C, 68·4; H, 8·8. $C_8H_{12}O_2$ requires C, 68·6; H, 8·65%); other physical properties are given in Table 1. The dione gave a reddish colour with ferric chloride in aqueous ethanol, and with formaldehyde in aqueous ethanol and a trace of piperidine gave *methylenebis*-4 : 4-*dimethyl*cyclo*hexane*-1 : 3-*dione*, m. p. 98—99°, $\lambda_{max.}$ 256 mμ (ε 26,300) (Found: C, 69·6; H, 8·2. $C_{17}H_{24}O_2$ requires C, 69·8; H, 8·3%).

3 : 3 : 5-*Trimethyl*cyclo*hexanone*.—*trans*-3 : 3 : 5-Trimethyl*cyclo*hexanol (45 g.) was added slowly with stirring to a mixture of sodium dichromate (60 g.), water (300 c.c.), and concentrated sulphuric acid (50 g.). The mixture was left for 20 hr., then extracted with ether, to give the ketone (36 g.), b. p. 71—73°/15 mm. The 2 : 4-dinitrophenylhydrazone was obtained in two forms: orange-yellow prisms (from glacial acetic acid), m. p. 147—148° (Found: N, 17·15. Calc. for $C_{15}H_{20}O_4N_4$: N, 17·5%); and yellow needles, m. p. 110°, from ethanol. Recrystallisation of the second form gave a mixture of the two and eventually transformation into the first was complete. The low-melting form appears to have been isolated by Braude and Evans [20] (m. p. 115—16°), and the high-melting form by Morgan and Hardy [21] (m. p. 145—147°).

[17] Bardhan, Banerji, and Bose, *J.*, 1935, 1127.
[18] Perkin, *J.*, 1902, 246.
[19] Blaise, *Bull. Soc. chim. France*, 1899, **21**, 626.
[20] Braude and Evans, *J.*, 1954, 613.
[21] Morgan and Hardy, *Chem. and Ind.*, 1933, 518.

Benzylideneisophorone (XI).—A mixture of freshly distilled *iso*phorone (30 g.), benzaldehyde (23 g.), ethanol (100 c.c.), and 45% aqueous sodium hydroxide (10 c.c.) was left for 7 days; the solution remained alkaline. Water was added, and the solid product (26 g.) was recrystallised from aqueous methanol. Benzylideneisophorone had m. p. 81—82°, $\lambda_{max.}$ 323·5 (ε 27,300) and 235 mμ (ε 7800) (Cornubert and Borrel [14] give m. p. 78·5—79°).

Benzylidene-(±)-piperitone (XII).—(±)-Piperitone (12·5 g.; purified through the sodium bisulphite adduct) and benzaldehyde (8·75 g.), in ethanol (30 c.c.), were added to a cold solution of sodium (0·5 g.) in ethanol (25 c.c.). The mixture was poured into water and slightly acidified; ether-extraction and distillation gave a syrup, b. p. 135—141°/0·05 mm., which gave crystals, m. p. 59·5—60·5°, from methanol (Read and Smith [22] give m. p. 61°). Light-absorption max. in EtOH: 324 (ε 31,000) and 234·5 mμ (ε 7300).

*Trimethylcyclohexenone Mixture.—trans-3 : 3 : 5-*Trimethyl*cyclo*hexanol (284 g.) and concentrated sulphuric acid (8 c.c.) were heated together at 160—185° (bath), the hydrocarbon distilling off as it was formed. Redistillation gave a mixture of trimethyl*cyclo*hexenes (170 g.), b. p. 130—138°, n_D^{17} 1·4419. This product (150 g.) was diluted with glacial acetic acid (350 c.c.), and a solution of chromium trioxide (24 g.) in water (150 c.c.) and acetic acid (675 c.c.) was added with stirring at 18—28°. The mixture was left for 24 hr., 50% aqueous potassium hydroxide (200 c.c.) added, and the oily product isolated by ether-extraction. Unchanged trimethyl*cyclo*hexene (52 g.) was obtained, together with a mixture of trimethyl*cyclo*hexenones (26 g.), b. p. 95—105°/20 mm., n_D^{22} 1·4641 (Found: C, 77·9; H, 10·4. Calc. for $C_9H_{14}O$: C, 78·2; H, 10·2%). A resin was formed with 2 : 4-dinitrophenylhydrazine; repeated crystallisation from aqueous acetic acid gave a small amount of *iso*phorone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 143—144° (Found: N, 17·3. Calc. for $C_{15}H_{16}O_4N_4$: N, 17·6%).

Dimethyl αxγ-Trimethylglutarate.—The trimethyl*cyclo*hexenone mixture (10 g.), sodium hydroxide (4 g.), and water (500 c.c.) were stirred at 0°, and 5% aqueous potassium permanganate (500 c.c.) was added dropwise. The solid was removed and the filtrate continuously extracted with ether for 24 hr. The resulting syrup (10 g.) was extracted with hot light petroleum (b. p. 40—60°), to yield *αxγ*-trimethylglutaric acid (3 g.), m. p. 97—98° (Found: equiv., 87·8. Calc. for $C_8H_{14}O_4$: equiv., 87·1) (Perkin and Smith [13] give m. p. 97—98°). The fraction insoluble in light petroleum was a lactonic acid of equivalent weight 187; oxidation of this (7 g.) gave further quantities of trimethylglutaric acid (3 g.), m. p. 97—98°. The dimethyl ester, obtained by boiling the acid with methanol and concentrated sulphuric acid, had b. p. 115—120°/15 mm., $n_D^{21\cdot5}$ 1·4309.

γ-Methoxycarbonyl-αγ-dimethylvaleric Acid (III; R = Me).—Dimethyl *αxγ*-trimethylglutarate (7·5 g.) and 0·5N-ethanolic potassium hydroxide (75 c.c.) were stirred at 20° for 21 hr., a small amount of solid was filtered off, and the alcohol removed at 30—40° in a vacuum. The residue was dissolved in water, extracted with ether, and acidified. The liberated *γ-methoxycarbonyl-αγ-dimethylvaleric acid* (4·2 g.), b. p. 150—160°/13 mm., $n_D^{18\cdot5}$ 1·4428, was isolated by means of ether (Found: C, 57·6; H, 8·8%; equiv., 195. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%; equiv., 188).

γ-Methoxycarbonyl-αγ-dimethylvaleroyl Chloride (IV; R = Me).—The above acid (3·7 g.) and thionyl chloride at 30—40° for 5 hr. gave the chloride (3 g.), b. p. 60—65°/2 mm., $n_D^{16\cdot5}$ 1·4451, which gave a *p-bromoanilide* (74%), m. p. 83—84° (Found: N, 4·0. $C_{15}H_{20}O_2NBr$ requires N, 4·1%).

Methyl 2 : 4 : 4-Trimethyl-5-oxohexanoate (VI; R = Me).—A Grignard solution from methyl bromide (7·0 g.), magnesium (1·7 g.), and ether (50 c.c.) was treated with anhydrous powdered cadmium chloride (7 g.). The ether was replaced with dry benzene (50 c.c.), and *γ*-methoxycarbonyl-αγ-dimethylvaleroyl chloride (2·8 g.) in benzene (20 c.c.) added with stirring. The mixture was stirred at 80° for 40 min., then ice and dilute hydrochloric acid added. Evaporation of the benzene gave an oil, which partly crystallised. Trituration with light petroleum (b. p. 40—60°) gave 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (0·3 g.), m. p. 130—131°, $\lambda_{max.}$ 258 mμ (ε 18,400) in EtOH, having an equivalent weight of 152 by electrometric titration; the m. p. was not depressed on admixture with the specimen described below. The light petroleum solution afforded *methyl 2 : 4 : 4-trimethyl-5-oxohexanoate* (1·4 g.), b. p. 95—105°/14 mm., n_D^{20} 1·4458 (Found: C, 64·35; H, 9·6. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·75%); the ester gave a positive iodoform test, and formed an oily 2 : 4-dinitrophenylhydrazine.

4 : 4 : 6-*Trimethyl*cyclo*hexane*-1 : 3-*dione* (VII; R = Me).—Sodium (1·0 g.) was converted into solvent-free sodium methoxide, which was suspended in dry ether (30 c.c.); methyl 2 : 4 : 4-trimethyl-5-oxohexanoate (0·9 g.) in dry ether (20 c.c.) was added, and the mixture stirred at

[22] Read and Smith, *J.*, 1921, 785.

20° for 20 hr. Ice-water was added, the solution extracted with ether and acidified with hydrochloric acid, and the precipitated oil (0·6 g.) isolated by ether. Recrystallisation from light petroleum (b. p. 60—80°) gave the *dione*, m. p. 130—131° (Found: C, 69·85; H, 8·8. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%); the substance gave a greenish-brown colour with ferric chloride in 50% ethanol; piperonaldehyde in aqueous ethanol containing a little piperidine gave the derivative, m. p. 191—193° (Gibson, Penfold, and Simonsen [1] give m. p. 192—193°). Light absorption and pK_a values for the dione are given in Table 1.

(±)-*Angustione* (IX).—**4 : 4 : 6-Trimethylcyclo**hexane-1 : 3-dione (0·5 g.), fused sodium acetate (0·2 g.), and acetic anhydride (5 c.c.) were refluxed for 7 hr. The acetic anhydride was removed at 15 mm., and the residue extracted with hot light petroleum (b. p. 60—80°). Distillation gave (±)-angustione, b. p. 130—140°/15 mm., characterised by the formation of an imine, m. p. 138—139° (from *cyclo*hexane) (Found: C, 67·75; H, 9·0. Calc. for $C_{11}H_{17}O_2N$: C, 67·65; H, 8·8%), and a greyish-blue copper salt, m. p. 201—202° (from light petroleum–benzene) (Cahn, Gibson, Penfold, and Simonsen [2] give m. p. 203—204°, and for the imine, m. p. 138—139°). The m. p. of the imine was not depressed on admixture with a specimen obtained from natural sources. The infrared spectra of the synthetic and the natural imine were practically identical.

The authors are indebted to Professor M. Stacey, F.R.S., for guidance and to Glaxo Laboratories Ltd. for a grant (to G. R. E.). They also thank Professor A. J. Birch for a specimen of (±)-angustione imine derived from natural sources, and Dr. D. H. Whiffen for infrared studies.

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786. *Researches on Acetylenic Compounds. Part LII.* The Preparation and Anomalous Absorption Spectra of Some* bicyclo[2 : 2 : 1]-*Heptane Derivatives.*†

By E. R. H. Jones, G. H. Mansfield, and M. C. Whiting.

Diels–Alder reactions between *cyclo*pentadiene and buta-2 : 3-dienoic and but-2-ynoic acid give unsaturated *bicyclo*heptane derivatives which show some unexpected spectroscopic properties. The structures of the products have been established, and the effects of molecular simplification upon these optical anomalies have been investigated.

The abnormal ultraviolet absorption spectra of 2 : 5-dihydro-aceto- and -butyro-phenones (maxima at unexpectedly long wavelengths and of reduced intensities), discovered by Bowden and Jones,[1] have initiated discussions of the absorption spectra of *cyclo*hexa-1 : 4-diene derivatives generally.[2,3,4] Diels–Alder reactions with but-2-ynoic and buta-2 : 3-dienoic acid have now been studied in order to prepare a range of crystalline adducts in which these effects could be further illustrated and elucidated.

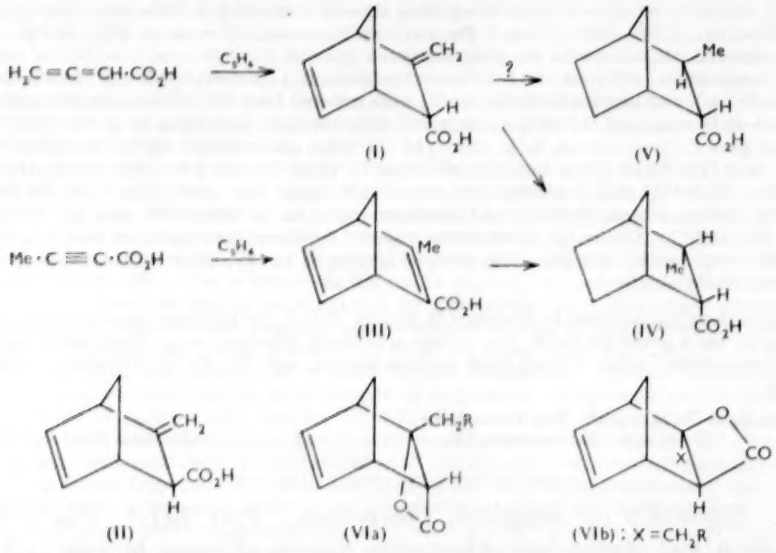
Buta-2 : 3-dienoic acid combined with butadiene at 60°, but no pure component could be isolated from the heterogeneous product. With *cyclo*pentadiene, even at 20°, an adduct was obtained for which the stereoisomeric structures (I) and (II), and structure (III), required consideration. The last was eliminated on spectroscopic grounds, and also by preparing an authentic specimen of this structure from but-2-ynoic acid by a reaction which proceeded only at 160°.

Direct application of Alder and Stein's rules [5] requires the formation of an adduct of structure (I), but formation of the isomer (II) either directly or by epimerisation of isomer

* Part LI, *J.*, 1955, 3636.
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Bowden and Jones, *J.*, 1946, 52.
[2] Braude, Jones, Sondheimer, and Toogood, *J.*, 1949, 607.
[3] Bartlett and Lewis, *J. Amer. Chem. Soc.*, 1950, **72**, 1005.
[4] Cram and Steinberg, *ibid.*, 1951, **73**, 5691.
[5] Alder and Stein, *Annalen*, 1934, **514**, 1; *Angew. Chem.*, 1937, **50**, 510.

(I) during the reaction is not entirely precluded. Hydrogenation of the adduct gave a liquid mixture of tetrahydro-derivatives from which one crystalline isomer was isolated in low (7%) yield, although the infrared spectra of the total hydrogenation product and of



the solid, as solutions, were virtually identical. (Since *bicyclo*heptane derivatives show extraordinarily large melting-point depression coefficients, the low yield of crystallisable material does not imply that very large quantities of other compounds were present.) Alder and his collaborators [6] have prepared all four stereoisomeric 2-methyl*bicyclo*[2 : 2 : 1]-heptane-3-carboxylic acids, and our specimen proved to be identical with that formulated as (IV). Thus the buta-2 : 3-dienoic acid adduct must have structure (I), and, as would be expected, the acid (IV) predominates over the higher-melting isomer (V) in the hydrogenation product. Hydrogenation of acid (III) gave the same crystalline tetrahydro-derivative in 40% yield, a result which confirms the configuration (IV) assigned [6] to it.

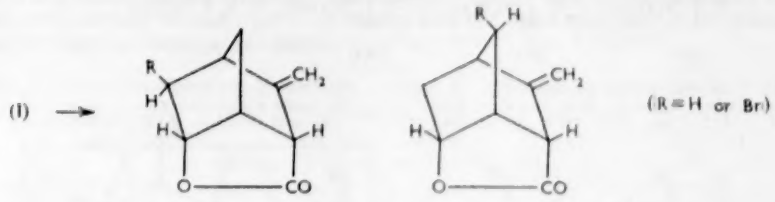
Treatment of acid (I) with bromine in sodium hydrogen carbonate solution gave a bromo-lactone, while the corresponding simple lactone was obtained with 50% sulphuric acid. These showed carbonyl bands in the infrared region at 1790 and 1780 cm.$^{-1}$ respectively, which eliminates the structures (VI) expected on Markownikow addition to the exocylic methylene group; indeed, provided that careful intensity measurements were made (see below), these infrared spectra also indicated that the latter grouping was still present in the molecule and that the endocyclic double bond was not. Ozonolysis gave about 20% yields of formaldehyde from each lactone, which confirms this conclusion. Upon the simplest postulates this would in turn prove the structures (VII; R = Br or H) for the lactones and (I) for the original adduct; but, if possible Wagner–Meerwein rearrangements are admitted,[7] lactones (VII) and (VIII) (identical when R = H) might be obtained similarly from an adduct of structure (II).

The effects of alkalis on the acids (I) and (III) were next examined in the hope of equilibrating acids (I—III). While acid (I) was stable to alkali, the characteristic ultraviolet absorption maxima of the isomer (III) were gradually lost in 9N-potassium hydroxide at 118°, and a 30% yield of the acid (I) was obtained. This isomerisation, to a product in which formal conjugation is destroyed and hyperconjugation is diminished, is a remarkable

[6] We are indebted to Professor K. Alder for kindly communicating to us his unpublished observations.

[7] See Berson and Swidler, *J. Amer. Chem. Soc.*, 1954, **76**, 4060, for a summary.

example of the predominance of Baeyer strain in such systems.[8] While the results are not entirely conclusive, it appears probable that in these experiments equilibrium between acids (I) and (II) was established, and that (II) was the less stable isomer and so was not formed in quantity. Although in saturated *bicyclo*heptane derivatives the *endo*- is normally less stable than the *exo*-form, introduction of an ethylenic linkage reduces steric crowding in the former and might also stabilise it through non-classical electronic interaction.



(VII) (VIII)

The adduct (I) could be esterified, and recovered by alkaline hydrolysis of the ester; the ester was also obtained directly from ethyl buta-2 : 3-dienoate and *cyclo*pentadiene, though in lower yield than when the free acid was used.[9] The ester of the adduct (III) rapidly became a glass when exposed to air at room temperature, whereas the ester of the isomer (I) is stable.

Ultraviolet absorption spectra reported below for the acids (I) and (III) were unexpected, and a number of compounds were therefore prepared in which the various structural peculiarities were introduced separately. Thus hydrogenation of (III) over platinum resulted in a diminution in uptake-rate after the absorption of 1 mol., and the conjugated acid (IX; R = Me), whose structure followed from its normal and unambiguous ultraviolet and infrared spectra, was readily isolated when uptake was interrupted. Treatment of *cyclo*pentadiene with propiolic acid at 0° as described by Alder *et al.*[10] gave adduct (X)—a striking contrast with the analogous but much slower reaction with but-2-ynoic acid. Unfortunately, semihydrogenation of (X) did not prove possible, even when palladium was used.

The ketone (XI) was prepared by heating but-3-yn-2-one with *cyclo*pentadiene as described by Petrov and Sopov.[11] It proved to be even more unstable than the esters of (III) and (X), and could not be regenerated from its semicarbazone. (It is therefore the only substance among the group discussed below which was not either crystalline itself or obtained by one very simple and mild reaction from a crystalline precursor.)

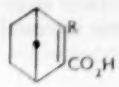
*cyclo*Hexa-1 : 3-diene did not react with but-2-ynoic acid even at 100°, but with propiolic acid it gave a 30% yield of the adduct (XII) at *ca.* 70°.

Butadiene reacted with but-2-ynoic and propiolic acid in benzene at 80° and 55° respectively, giving the adducts (XIII; R = Me) (4%) and (XIII; R = H) (8%); at 170° with propiolic acid the only product (34%) was benzoic acid. The dihydrobenzoic acid (XIII; R = H) was reported by Alder and Backendorf [12] as a product of the reaction between butadiene and acetylenedicarboxylic acid, but its structure was not then proved rigorously. The spectrographic results below clearly differentiate acids (XIII) from their aromatic analogues and, though abnormal, are consistent with these structures in view of the spectrum of the acid (III); they are quite inconsistent with the fully conjugated alternatives, which would imply absorption maxima near 3000 Å. On hydrogenation, acid (XIII; R = H) smoothly gave *cyclo*hexanecarboxylic acid.

Hydrogenation of acid (XIII; R = Me) over palladium gave the acid (XIV; R = Me).[13]

[8] Cf. Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.
[9] Cf. Holmes, *Org. Reactions*, 1948, **4**, 71.
[10] Alder and Stein, *Annalen*, 1936, **525**, 183.
[11] Petrov and Sopov, *J. Gen. Chem. U.S.S.R.*, 1953, **23**, 1085 (*Zhur. obshchei Khim.*, 1953, **23**, 1034).
[12] Alder and Backendorf, *Ber.*, 1938, **71**, 2199.
[13] Kay and Perkin, *J.*, 1905, **87**, 1066.

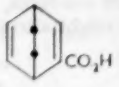
Penta-2 : 3-dienedioic acid (previously termed "glutinic acid" and formulated as pent-2-ynedioic acid) [14] reacted with *cyclo*pentadiene at 35°, giving a normal adduct (XVIII), the properties and conditions of formation of which confirm the revised structure [14] of the parent acid.



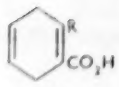
(IX)

(X)

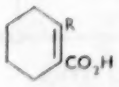
(XI)



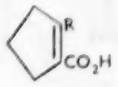
(XII)



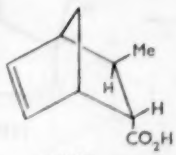
(XIII)



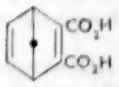
(XIV)



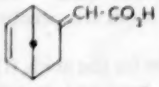
(XV)



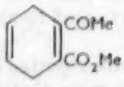
(XVII)



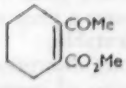
(XVI)



(XVIII)



(XIX)



(XX)

Ultraviolet Absorption Spectra.—The ultraviolet spectra, observed under comparable conditions, are shown in Figs. 1 and 2 and in the Table. Our data for acids (XIV; R = H) and (XV; R = Me) agree well with the results of Ungnade and Ortega [15] and Eglinton

Ultraviolet absorption spectra.

	R = H		R = Me		
	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$	Δ_{Me} (Å)
	(*a*) *Acids.*				
(XIV)	2170	10·3	2250	9·2	80
(XV)	2220	11·5	2320	11·1	100
(IX)	—	—	2340	8·1	—
(XIII)	(at 2015 Å, ε 6000)		(at 2045 Å, ε 6000)		~30
	2360	2·1	2360	2·55	0
(X, III)	(at 2000 Å, ε 11,000)		2030	8·7	>30
	2290	3·7	2310	3·8	20
	~2650	~1·5	2670	2·35	~0
(XII)	(at 2020 Å, ε 7800)				
	2240	7·8			
	(*b*) *Ketones.*				
1-Acetyl*cyclo*hexene and its 2-Me deriv.[3]	2320	12·5	2490	6·9	170
1-Acetyl*cyclo*pentene and its 2-Me deriv.[20]	2390	13	2530	10	140
2 : 5-Dihydroacetophenone and its 6-Me deriv.	2450	4	2450	5	0
(XI)	(at 2000 Å, ε 6750)				
	2400	5·3			
	2760	1·75			
	(*c*) *Related compounds.*				
(XVI)	(at 2000 Å, ε 13,000)				
	2470	5·15			
(XVIII)	2190	12			
(XIX)	(at 2150 Å, ε 3000)				
	2450	2·0			
(XX)	2200	6·0			

[14] Jons, Mansfield, and Whiting, *J.*, 1954, 3208.
[15] Ungnade and Ortega, *J. Amer. Chem. Soc.*, 1951, **73**, 1564.

and Whiting,[16] respectively. The position of $\lambda_{max.}$ now reported for *cyclo*pent-1-ene-carboxylic acid (XV; R = H), however, differs significantly from that reported earlier by Braude and Forbes.[17] Professor E. A. Braude, who very kindly provided the specimen used here, has also redetermined the absorption spectrum, and reports $\lambda_{max.}$ 2215 Å (ε 11,200), in excellent agreement with our results. For acid (XIV; R = Me), our data agree poorly with those reported, for a specimen of undisclosed physical constants and method of preparation, by Ungenade and Ortega,[15] but in view of the simplicity of our preparative method, and the good agreement with the other constants in the literature, we believe that our results are authentic.

FIG. 1. *Ultraviolet absorption of acids (in 95% ethanol) with β-hydrogen atoms (in formulæ* XIII, XIV, *and* XV, R = H).

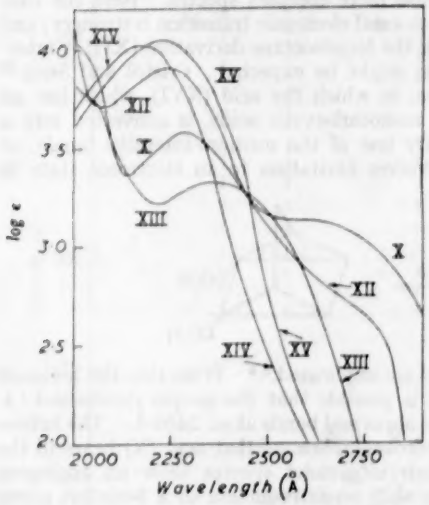
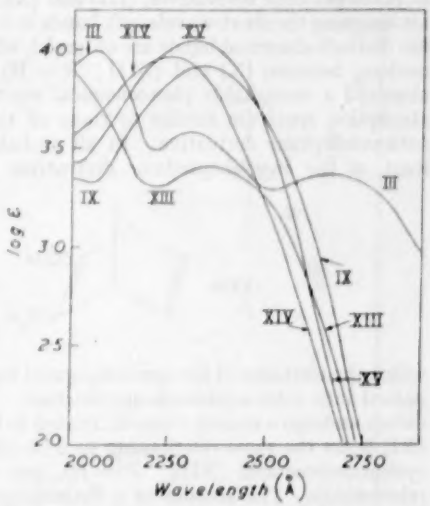
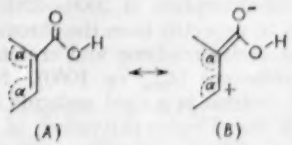


FIG. 2. *Ultraviolet absorption spectra of acids (in 95% ethanol) with β-methyl substituents (in formulæ* IX, XIII, XIV, *and* XV, R = Me).



The spectra of the monoethylenic reference compounds (XIV, XV, and IX; R = Me) illustrate neatly the effects of Baeyer strain. In a cyclic αβ-ethylenic acid a reduction in the angle α, consequent upon the closing of a ring and the introduction of strain, will increase the importance of canonical form *B* relatively to *A* (see Brown, Brewster, and Shechter[18]). In such a weakly polarised system the latter is of course the more important,



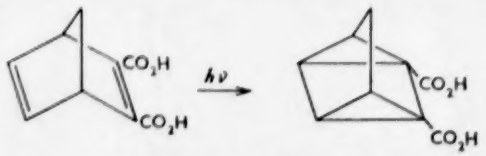
(*A*) (*B*)

and the change is towards equality; it will therefore stabilise the excited state preferentially, and displace the absorption maximum bathochromically [19]—hence the observed ascending order for $\lambda_{max.}$ values. (A somewhat similar discussion of the spectra of αβ-ethylenic ketones has recently appeared.[20]) The values of $\Delta\lambda_{max.}$ for β-substitution of a methyl

[16] Eglinton and Whiting, *J.*, 1953, 3025.
[17] Braude and Forbes, *J.*, 1951, 1775.
[18] Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.
[19] Brooker, Keyes, Sprague, Van Dyke, Van Lare, Van Zandt, White, Cressman, and Dent, *ibid.*, 1951, **73**, 5332.
[20] Schubert and Sweeney, *ibid.*, 1955, **77**, 2297.

group are +80 and +100 Å in the *cyclo*hexene and *cyclo*pentene derivatives, respectively. The corresponding acyclic compounds, 3-methylbut-2-enoic (tiglic) and 2 : 3-dimethylbut-2-enoic acid, have $\lambda_{max.}$ 2125 and 2210 Å, respectively,[21] giving $\Delta\lambda_{max.}$ 85 Å.

Introduction of a second, unconjugated ethylenic linkage into structures of type (XIV), giving (XIII), profoundly changes the spectrum. Both *cyclo*hexa-1 : 4-diene derivatives (XIII) show bands at 2360 Å; but in view of their low intensities and the absence of the usual bathochromic effect of methyl substitution, there seems little reason to consider these bands as representing the normal electronic transitions of αβ-ethylenic acids, which occur at 2170 and 2250 Å in the reference *cyclo*hexenes. On the contrary, the 2170 and 2250 Å bands may more profitably be compared with the bands with maxima just below 2000 Å for (XIII), which show intensities of the right order of magnitude and some indication of a bathochromic shift on substitution of methyl for hydrogen. The two *bicyclo*heptadiene derivatives, (III) and (X), show more complex spectra. Here the case for assigning the short-wavelength bands to the normal electronic transition is stronger; and *two* distinct abnormal bands are observed, while the *bicyclo*octane derivative (XII) is intermediate between (X) and (XIII; R = H), as might be expected. Cristol and Snell[22] observed a remarkable photochemical reaction, in which the acid (XVI), which has an absorption spectrum similar to those of the monocarboxylic acids, is converted into a *tetracyclo*heptane derivative. In all probability one of the medium-intensity bands, at least, of the *bicyclo*heptadiene derivatives involves excitation to an electronic state in

(XVI) 

which the electrons of the non-conjugated bond are implicated.[3,4] From this the molecule passed into a *tetracyclo*heptane structure. It is possible that the simple *cyclo*hexa-1 : 4-dienes undergo a similar reaction, related to the abnormal bands at *ca.* 2400 Å. The ketone (XI) bears the same relationship to 2 : 5-dihydroacetophenone that acid (X) bears to the *cyclo*hexadiene-acid (XIII; R = H), and their ultraviolet spectra show an analogous relationship. The absence of a bathochromic shift on introduction of a β-methyl group into 2 : 5-dihydroacetophenone [2] parallels the observations above. In these ketones, also, the medium-intensity bands should therefore be ascribed [4] to abnormal transitions directly involving the non-conjugated bond, rather than to a displacement of the normal αβ-ethylenic ketone band through hyperconjugation; almost certainly examination of the 2000—2200 Å region would reveal a second absorption band in these cases, as in that of (XI).

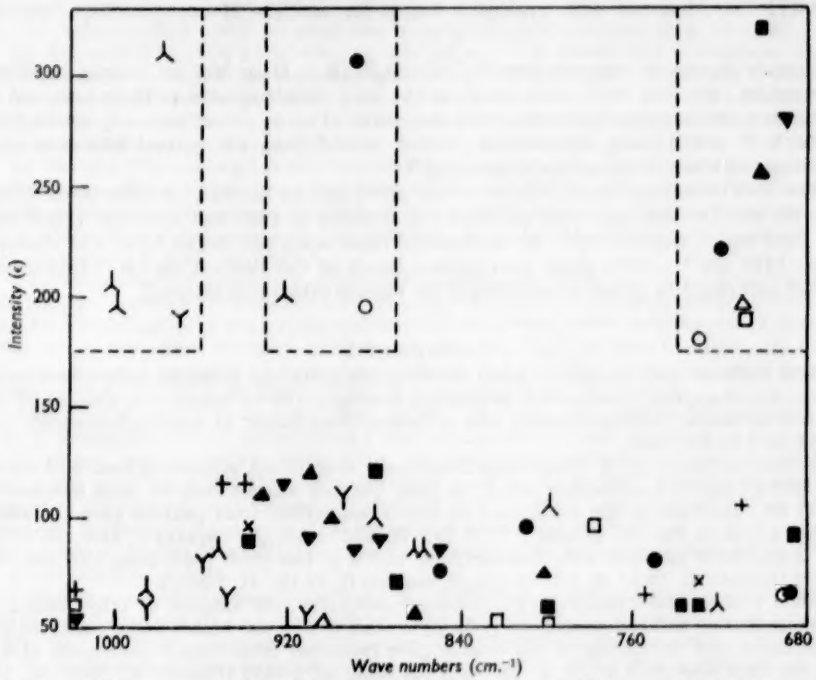
The adduct (I) showed end-absorption at 2000—2200 Å appreciably more intense (ε 8000 at 2000 Å) than would be expected from the chromophores present, and even the adduct (XVII) prepared from *cyclo*pentadiene and crotonic acid absorbed much more strongly (ε_{2000} 5100) than *cyclo*hexene (ε_{2000} *ca.* 1000). Some non-classical interaction between adjacent unsaturated systems in a rigid molecule is probably general; complete saturation of the rings as in the dihydro-derivative of the lactone (VII; R = H), obtained by acid cyclisation of (XVII), naturally resulted in virtual transparency even near 2000 Å.

Infrared Absorption Spectra.—These also presented several points of interest. The di- and tri-cyclic compounds all have unusually rigid molecules, and this presumably explains the exceptional number of sharp, intense bands observed in the "fingerprint" region, *i.e.*, 660—1200 cm.$^{-1}$. In such molecules, any "skeletal" (*i.e.*, C–C deformation or stretching) vibration must be communicated to the polar groups, and will therefore cause a considerable change in dipole moment and thus correspond to an intense infrared

[21] Braude and Evans, *J.*, 1955, 3331.
[22] Cristol and Snell, *J. Amer. Chem. Soc.*, 1954, **76**, 5000.

band.[23] Similarly, any change in the intramolecular strains (*e.g.*, as a result of hydrogenating an ethylenic linkage) would be expected to affect the frequency of these skeletal modes. Thus, whereas it is usually possible to pick out olefinic C–H out-of-plane deformation bands by inspection, because they are so much more intense than the various C–C deformation bands, etc., and because they disappear on hydrogenation, this was impossible with the spectra of the compounds discussed above, even where those of the corresponding dihydro-derivatives were available for comparison. When, however, "apparent" molar extinction coefficients (*i.e.*, neglecting slit-width and false energy corrections, but allowing for base-line errors) were calculated, and the results plotted

FIG. 3. *Infrared maxima of* bicyclo*heptane derivatives* (*in* CS_2).



Symbol	Substance	Symbol	Substance	Symbol	Substance
●	(I)	○	Me ester of (I)	+	(IX; R = Me)
■	(III)	□	Me ester of (III)	▼	(X)
▲	(XVII)	△	Me ester of (XVII)	Y	(didydro VII; R = H)
×	(IV)	⅄	(VII; R = H)		

(Fig. 3), it was at once possible to identify these bands by their appreciably (but not overwhelmingly) greater intensities. These maxima fall within the broken lines in Fig. 3.

All compounds believed on chemical grounds to possess the groupings *cis* $HC^{!}=C^{!}H$ and/or $H_2C=C<$ showed *one* band (for each) with $\varepsilon > 180$ in the regions (680—740 and 870—930 cm.$^{-1}$, respectively) normal for these modes. Except for the tricyclic lactones (see below), none of the bands attributable to skeletal vibrations had $\varepsilon > 120$. Thus, despite the approximate nature of the methods used for measuring intensities, the results (uncertain to perhaps $\varepsilon \pm 20$, with most of the sources of error acting similarly on all bands in a given region) were of real value. The overtone ethylenic C–H out-of-plane deformation bands at *ca.* 1790 cm.$^{-1}$ were, of course, superimposed in the spectra of the lactones (VII; R = H

[23] R. N. Jones, Nolin, and Roberts, *J. Amer. Chem. Soc.*, 1956, **77**, 6331.

and Br) on the intense carbonyl bands, and the >C=C< stretching modes were barely distinguishable at *ca.* 1680 cm.$^{-1}$, an abnormal frequency not unexpected in view of the strained environment of the methylene group. The region below 1000 cm.$^{-1}$ was thus the only one available for structural confirmation of these lactones.

In the unbridged *cyclo*hexa-1 : 4-diene derivatives (XIII; R = Me and H), and the methyl ester of the latter, the *cis*-CH=CH– out-of-plane deformation mode was probably represented by the intense absorption below 670 cm.$^{-1}$ at the transmission limit of the available sodium chloride prism.

The tricyclic lactones (VII; R = H and Br) and some related tricyclic lactones [24] showed intense and sometimes complex absorption at 970—1000 cm.$^{-1}$. This might be confused with an ethylenic out-of-plane deformation band due to the grouping *trans*-CH=CH–, but not with analogous bands for *cis*-CH=CH– or >C=CH$_2$. In the compounds possessing the grouping H–C(=C)–CO$_2$R (R = H or Me) an intense band was observed at 750—775 cm.$^{-1}$, near bands in the very simple spectra of tiglic acid and its ethyl ester, which have the same partial structure. This is almost certainly attributable to the C–H out-of-plane deformation process, moved from the normal 800—840 cm.$^{-1}$ region by the effect of the carboxyl grouping.[25]

The C=O stretching bands (dimer) of the unbridged *cyclo*hexa-1 : 4-diene acids (XIII; R = Me and H) were split into well-resolved doublets at 1685 and 1669 cm.$^{-1}$, and 1687 and 1665 cm.$^{-1}$, respectively. In the bridged diene-acids one broad band was observed at *ca.* 1670 cm.$^{-1}$. With these reservations, bands in the 1600—1750 cm.$^{-1}$ region were normal and could be taken as confirming the various structures assigned.

Experimental

Acid fractions were normally isolated *via* saturated potassium hydrogen carbonate solution. Ultraviolet absorption spectra were determined in 95% EtOH by means of a Unicam SP 500 spectrophotometer; infrared spectra with a Perkin-Elmer Model 21 spectrophotometer; and m. p.s on a Kofler block.

3-*Methylene*bicyclo[2 : 2 : 1]*hept-5-ene-2-carboxylic Acid* (I).—A solution of buta-2 : 3-dienoic acid (2·0 g.) and *cyclo*pentadiene (4·3 g.) in ether (10 c.c.) was set aside at room temperature for 12 hr. Isolation of the acidic fraction and crystallisation from pentane gave the *adduct* (I) (3·0 g.), m. p. 69—70° (Found: C, 71·75; H, 6·55. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%). The *methyl* ester, prepared with diazomethane, had b. p. 100—105° (bath-temp.)/10 mm., $n_D^{14\cdot5}$ 1·4950 (Found: C, 73·1; H, 7·1. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%).

Ethyl 3-*Methylene*bicyclo[2 : 2 : 1]*hept-5-ene-2-carboxylate.*—A solution of ethyl buta-2 : 3-dienoate (2·24 g.) and *cyclo*pentadiene (1·32 g.) in ether (5 c.c.) was heated under reflux for 2 hr. Evaporation and distillation of the residue gave recovered ethyl buta-2 : 3-dienoate (1·3 g.) and the *ethyl ester* (0·58 g.), b. p. 105—107°/21 mm., n_D^{15} 1·4832 (Found: C, 73·9; H, 7·85. $C_{11}H_{14}O_2$ requires C, 74·15; H, 7·9%). Hydrolysis with 10% aqueous potassium hydroxide (2 hr. at 90°) gave a 70% yield of the corresponding acid.

3-*Methylene*-6-*hydroxy*bicyclo[2 : 2 : 1]*heptane*-2-*carboxylic Lactone* (VII; R = H).—The above acid (I) (350 mg.) was shaken with sulphuric acid (10 c.c., 50%) for 3 hr. at 20°. Isolation of the neutral fraction and crystallisation from pentane gave the very volatile *lactone* (240 mg.), m. p. 49·5—50·5° (Found: C, 72·0; H, 6·7. $C_9H_{10}O_2$ requires C, 72·0; H, 7·0%). Ozonolysis of 260 mg. in acetic acid (40 c.c.) for 1 hr. gave formaldehyde, identified as its dimedone derivative (120 mg.), m. p. and mixed m. p. 187—190°.

5-*Bromo*-3-*methylene*-6-*hydroxy*bicyclo[2 : 2 : 1]*heptane*-2-*carboxylic Lactone* (VII; R = Br).—A solution of the acid (I) (200 mg.) in saturated sodium hydrogen carbonate (5 c.c.) was treated with bromine (210 mg.) in carbon tetrachloride (5 c.c.). Evaporation of the organic layer and crystallisation from benzene–light petroleum (b. p. 40—60°) gave the *bromo-lactone* (210 mg.), m. p. 77—78° (Found: 47·0; H, 4·15. $C_9H_9O_2Br$ requires C, 47·2; H, 3·95%). Ozonolysis of 290 mg. as above gave the dimedone derivative (80 mg.) of formaldehyde.

3-*Methyl*bicyclo[2 : 2 : 1]*hepta*-2 : 5-*diene*-2-*carboxylic Acid* (III).—But-2-ynoic acid (5·0 g.) and di*cyclo*pentadiene (10·0 g.) were heated under reflux in nitrogen for 2·5 hr. The acid fraction

[24] Henbest and Nicholls, unpublished work.
[25] Freeman, *J. Amer. Chem. Soc.*, 1953, **75**, 1859; Allan, Meakins, and Whiting, *J.*, 1955, 1874.

was crystallised from water, giving the *acid* (III) (2·0 g.), m. p. 92° (Found: C, 72·0; H, 6·7. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%). The *methyl* ester, prepared using diazomethane, had b. p. 55° (bath-temp.)/0·05 mm., n_D^{20} 1·4962 (Found: C, 72·5; H, 7·45. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%).

When this acid (500 mg.) was heated with 9N-potassium hydroxide (50 c.c.) at 118° for 10 min., and the acid fraction was isolated, crystallisation from pentane gave the isomeric acid (I) (170 mg.), m. p. and mixed m. p. 69—70°.

Hydrogenation Experiments.—(*a*) The acid (I) (2·7 g.), pre-reduced platinic oxide (0·1 g.), and ethanol (30 c.c.) were shaken until absorption ceased (910 c.c. at 20°/752 mm.). Filtration and evaporation gave an oil which was dissolved in pentane and cooled to −70°; the solid was then separated by means of a pipette. After five crystallisations from pentane at −70° the solid obtained (*ca.* 700 mg.) melted constantly at 31—35°. It was dried, pressed on porous porcelain at 20°, and crystallised twice more from pentane, giving 180 mg. of acid (IV), m. p. 51—53°, raised to 54·5—55·5° on admixture with an authentic specimen (m. p. 57—58°).

(*b*) The acid (III) (1·00 g.) in ethyl acetate (40 c.c.) was shaken with pre-reduced platinic oxide (0·1 g.) in hydrogen, 324 c.c. being absorbed at 24·5°/753 mm. Filtration, evaporation of the solvent, distillation, and crystallisation from pentane at −70° gave the saturated acid (IV) (0·40 g.), m. p. 47—49°, raised to 54° on recrystallisation and undepressed on admixture with an authentic sample (Found: C, 70·3; H, 9·3. Calc. for $C_9H_{14}O_2$: C, 70·1; H, 9·15%).

(*c*) The acid (III) (500 mg.) in ethyl acetate (40 c.c.) was shaken in hydrogen with pre-reduced platinic oxide (50 mg.) until 84 c.c. had been absorbed at 23°/747 mm., whereafter the rate of uptake decreased. Evaporation, distillation, and crystallisation at −70° gave 3-*methyl*bicyclo-[2 : 2 : 1]*hept*-2-*ene*-2-*carboxylic acid* (IX) (130 mg.), m. p. 41—44° (Found: C, 71·05; H, 8·05. $C_9H_{12}O_2$ requires C, 71·0; H, 7·95%).

3-*Carboxymethylene*bicyclo[2 : 2 : 1]*hept*-5-*ene*-2-*carboxylic Acid* (XVIII).—*cyclo*Pentadiene (330 mg.) and penta-2 : 3-dienedioic acid (640 mg.) in ether (10 c.c.) were heated under reflux for 2 hr. Evaporation of the solvent and crystallisation from water gave the *adduct* (900 mg., 93%), m. p. 235—236° (Found: C, 61·8; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%). The *dimethyl ester*, prepared by using diazomethane, had b. p. 95° (bath-temp.)/0·01 mm., n_D^{15} 1·5092 (Found: C, 64·35; H, 6·25. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%).

cyclo*Hexa*-1 : 4-*diene*-1-*carboxylic Acid* (XIII; R = H).—A mixture of propiolic acid (5·0 g.), butadiene (10 c.c.), quinol (0·1 g.), and benzene (10 c.c.) was heated in an autoclave to 55° for 15 min., then set aside at 20° for 60 hr. Isolation of the acidic fraction and crystallisation from water gave the acid (XIII; R = H) (0·72 g., 8%), m. p. 122°, strongly depressed on admixture with benzoic acid (Found: C, 67·9; H, 6·6. $C_7H_8O_2$ requires C, 67·75; H, 6·5%). Alder and Backendorf [13] give m. p. 123° for an acid believed to be (XIII; R = H). Catalytic hydrogenation (uptake 2 mols.) gave *cyclo*hexanecarboxylic acid, charactised as its amide, m. p. and mixed m. p. 184°.

2-*Methyl*cyclo*hexa*-1 : 4-*diene*-1-*carboxylic Acid* (XIII; R = Me).— A mixture of but-2-ynoic acid (7·4 g.), butadiene (16 c.c.), quinol (0·1 g.), and benzene (10 c.c.) was heated in an autoclave at 60—100° for 16 hr. Extraction with potassium hydrogen carbonate solution, acidification, and crystallisation of the precipitate from pentane gave the *adduct* (0·5 g., 4%), m. p. 132° (Found: C, 69·8; H, 7·4. $C_8H_{10}O_2$ requires C, 69·55; H, 7·3%). Continuous extraction of the aqueous filtrate with ether gave but-2-ynoic acid (5·2 g.).

2-*Methyl*cyclo*hex*-1-*ene*-1-*carboxylic Acid* (XIV; R = Me).—The above acid (87 mg.) in ethanol (20 c.c.) was shaken in hydrogen in the presence of 2% palladium–calcium carbonate until 16·0 c.c. were absorbed at 18°/750 mm. Filtration, evaporation, and crystallisation from water gave the acid (XIV; R = Me) (43 mg.), m. p. 87°. Kay and Perkin [13] give m. p. 87°.

2-*Acetyl*bicyclo[2 : 2 : 1]*hepta*-2 : 5-*diene* (XI).—But-3-yn-2-one (2·0 g.) and *cyclo*pentadiene (3·0 g.) were heated under reflux for 4 hr. Distillation gave the *adduct* (XI), b. p. 76° (bath-temp.)/0·1 mm., n_D^{23} 1·5070 (Found: C, 80·5; H, 6·95. $C_9H_{10}O$ requires C, 80·55; H, 7·5%). The lemon-yellow 2 : 4-*dinitrophenylhydrazone*, m. p. 133—134°, was crystallised from aqueous ethanol, and had $\lambda_{max.}$ 3650 Å (ε 20,500) (Found: N, 17·8. $C_{15}H_{14}O_4N_4$ requires N, 17·85%). The *semicarbazone* crystallised from aqueous ethanol, decomposed at 195°, and showed maxima at 2350 and 2840 Å (ε 10,000 and 15,700, respectively) (Found: C, 62·55; H, 6·7. $C_{10}H_{13}ON_3$ requires C, 62·8; H, 6·85%).

Petrov and Sopov [11] give b. p. 92°/20 mm., n_D^{20} 1·5098, for the ketone, in good agreement with the data given above; but for the 2 : 4-dinitrophenylhydrazone and semicarbazone they report m. p. 182·5—183·5° and 166—167°. They were unable to recrystallise the latter; and they noted (and explained) the polymerisation (dimerisation) of the parent ketone.

bicyclo[2 : 2 : 1]*Octa*-2 : 5-*diene*-2-*carboxylic Acid* (XII).—A mixture of propiolic acid (1·0 g.), *cyclo*hexa-1 : 3-diene (1·5 g.), and dioxan (5 c.c.) was heated under reflux for 12 hr. Isolation of the water-insoluble acidic fraction gave an oil which was extracted with boiling light petroleum (b. p. 60—80°) : the solid which separated was recrystallised from water, giving the *acid* (XII) (0·6 g.), m. p. 78—80° (Found : C, 71·7; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

We thank Mr. E. S. Morton and Mr. H. Swift for microanalyses, and Miss W. Peadon and Mrs. J. Shallcross for spectroscopic data.

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787. *Researches on Polyenes. Part IV.* The ω-p-Methoxyphenyl-polyene Aldehydes and their Absorption Spectra.†*

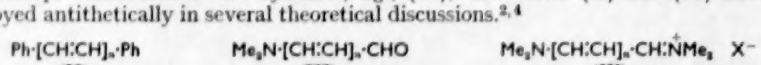
By D. MARSHALL and M. C. WHITING.

A series of ω-*p*-methoxyphenyl-polyene aldehydes (I; n = 1—7) has been prepared by use of a chain-extension method whereby two ethylenic bonds are added without isolation of intermediates. The electronic absorption spectra of the aldehydes are recorded and discussed.

FOR a projected synthesis of the fungal pigment cortisalin [1] the ω-*p*-methoxyphenyl-polyene aldehydes (I; n = 2, 4, and 6) were required as intermediates. Together with homologues with odd values of n these constitute an interesting series for the investigation

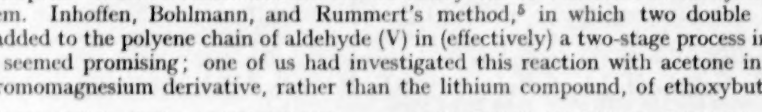
(I)

of relationships between electronic absorption spectra and chain-length in conjugated systems, in that they are intermediate between symmetrical, unpolarised polyenes, such as (II),[2] and highly polarised merocyanines,[3] such as (III). The latter approximate in spectroscopic behaviour to the cyanines, *e.g.*, (IV),[3] and series (II) and (IV) have been employed antithetically in several theoretical discussions.[2,4]



(II) (III) (IV)

A stepwise chain-extension method was obviously the best solution to the synthetical problem. Inhoffen, Bohlmann, and Rummert's method,[5] in which two double bonds were added to the polyene chain of aldehyde (V) in (effectively) a two-stage process in 50% yield, seemed promising; one of us had investigated this reaction with acetone in 1948, the bromomagnesium derivative, rather than the lithium compound, of ethoxybutenyne



(V)

(R = 2 : 6 : 6-trimethylcyclohexenyl)

being employed successfully. Methoxybutenyne, now commercially available, was condensed with *p*-methoxybenzaldehyde, and after addition of ethanol (with the aim of decomposing the complex; the effect was apparently favourable, although this may not

* Part III, *J.*, 1955, 3037.
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Marshall and Whiting, *Chem. and Ind.*, 1954, 1451.
[2] Lewis and Calvin, *Chem. Rev.*, 1939, **25**, 237.
[3] Brooker, Keyes, Sprague, Van Dyke, Van Lare, Van Zandt, and White, *J. Amer. Chem. Soc.*, 1951, **73**, 5326 *et seq.*
[4] Bayliss, *Quart. Rev.*, 1952, **6**, 319, and references there cited.
[5] Inhoffen, Bohlmann, and Rummert, *Annalen*, 1950, **569**, 226.

have been the true reason) lithium aluminium hydride was added.[6] Decomposition of the excess of hydride and addition of mineral acid gave the diene-aldehyde (I; $n = 2$) in a single stage. Under optimal conditions, with tetrahydrofuran as solvent, the yield was 52%. This aldehyde has been described [7] as a yellow oil; as now obtained, it crystallised at once and melted at 80°. From infrared data it was clearly the *trans-trans*-isomer.

$$MeO{\cdot}C_6H_4{\cdot}CHO + BrMg{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}OMe \longrightarrow [MeO{\cdot}C_6H_4{\cdot}CH(OMgBr){\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}OMe]$$

$$\downarrow$$

$$MeO{\cdot}C_6H_4{\cdot}[CH{:}CH]_2{\cdot}CHO + MeOH \longrightarrow [MeO{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}OMe]$$

This method is probably general and is the quickest yet described for the conversion, $R{\cdot}CHO \longrightarrow R{\cdot}[CH{:}CH]_2{\cdot}CHO$. Applied to benzaldehyde, for example, it gave a 75% yield of 5-phenylpenta-2 : 4-dienal, which at once crystallised, though most earlier workers [8] describe this compound as a liquid. Octa-2 : 4 : 6-trienal was similarly converted into dodeca-2 : 4 : 6 : 8 : 10-pentaenal in 27% yield. In series (I), *p*-methoxycinnamaldehyde gave (I; $n = 3$) in 46% yield, while the dienal itself gave the corresponding tetraenal in 26% yield. Beyond this point the yield fell sharply, despite variations in reaction conditions; for the aldehydes ($n = 5$ and 6), respectively, to 2% and 0·05%, the extreme insolubility of the latter alone making isolation possible. In these cases, however, the intermediate acetylenic alcohols (VI) were readily isolated in good yield and purified.

$$MeO{\cdot}C_6H_4{\cdot}[CH{:}CH]_n{\cdot}CHO \longrightarrow MeO{\cdot}C_6H_4{\cdot}[CH{:}CH]_n{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}OMe \quad (VI)$$

$$\downarrow$$

$$MeO{\cdot}C_6H_4{\cdot}[CH{:}CH]_{n+2}{\cdot}CHO$$

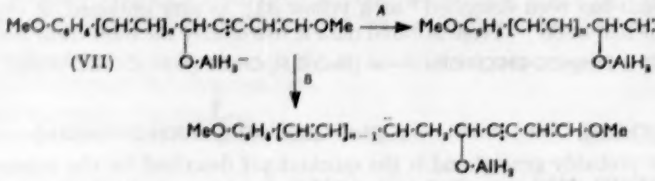
Hydrogenation with a partially poisoned palladium catalyst,[9] and treatment with aqueous oxalic acid gave the homologous aldehydes (I; $n = 5$ and 6) in 51 and 34% yield, respectively. Rather less satisfactory results were obtained when mineral acids were employed in the final stage, probably because these react with the acetylenic alcohols (VI), a little of which remained.

Condensation of the pentaenal with methoxybutenyne was difficult because of the insolubility of the aldehyde in the reaction mixture, and the product, though having the expected ultraviolet absorption spectrum, was itself very sparingly soluble. After hydrogenation and acid treatment, the heptaenal was obtained in 13% yield from the pentaenal. Clearly further extension of the polyene chain would require modification of the method. The aldehydes (I; $n = 5$ and 6) obtained by the two variants were identical, all showing intense absorption near 1000 cm.$^{-1}$ and very little at 650—850 cm.$^{-1}$; they were thus all-*trans*-compounds,[10] despite the fact that in the preparation of the higher members of the series *cis*-ethylenic linkages must have been present in their immediate precursors. This agrees with earlier work.[11]

The rapid decline in the yield given by the chemical reduction method, as the value of n in the starting material increases from 2 through 3 to 4, requires comment. When the alcohol (VI; $n = 4$) was isolated, and then treated with lithium aluminium hydride in a separate experiment, again only a minute yield of the aldehyde (I; $n = 6$) was formed. Perhaps the most reasonable explanation is that the intermediate complex (VII) can transfer a hydride ion either (*A*) to the adjacent acetylenic carbon atom, or (*B*) to the first carbon atom of the polyene chain. The longer the chain, the more will the carbanion formed by route (*B*) be stabilised relative to that formed by process (*A*). The fact that octa-2 : 4 : 6-trienal gives dodeca-2 : 4 : 6 : 8 : 10-pentaenal in 27% yield, as against the 2% yield when the methyl group is replaced by *p*-methoxyphenyl, is also explained by the potential electron-sink character of the aromatic system.

[6] Cf. Chanley and Sobotka, *J. Amer. Chem. Soc.*, 1949, **71**, 4140; Bates, Jones, and Whiting, *J.*, 1954, 1854.
[7] Vorländer and Gieseler, *J. prakt. Chem.*, 1929, **121**, 237.
[8] Kethur, Klein, and Wietbrock, *Ber.*, 1936, **69**, 2078; cf. Kuhn and Wintersteiner, *Helv. Chim. Acta*, 1929, **12**, 493.
[9] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[10] Allan, Meakins, and Whiting, *J.*, 1955, 1874.
[11] Braude and Coles, *J.*, 1951, 2085.

The *p*-methoxyphenyl-polyene aldehydes are all highly crystalline, relatively insoluble, and stable to oxygen, in the solid state at least, at moderate temperatures. Reduction of the aldehyde (I; $n = 2$) to the primary alcohol gave a compound which rapidly suffered



atmospheric oxidation. Even the methyl esters corresponding to series (I) were somewhat less stable; clearly the mesomeric effect illustrated plays a considerable part in this stabilisation, although crystal lattice forces are doubtless important too. The solubilities of the aldehydes (I; $n = 5$, 6, and 7) in chloroform at 25° were determined spectroscopically, values of 3·5, 0·4, and 0·05 g./l. being obtained, solubility thus decreasing by a factor of 8 for each additional ·CH:CH· group in the chain. Extrapolation suggests that absorption spectra could still be determined for (I; $n = 8$ and 9), but hardly for the decaenal, and not at all for higher homologues.

The ultraviolet absorption spectra of the aldehydes (I) are tabulated below and

TABLE. *Light-absorption maxima in chloroform.*

n	$\lambda_{max.}$ (Å)	$10^3\varepsilon$	$\lambda_{max.}$ (Å)	$10^3\varepsilon$	$\lambda_{max.}$ (Å)	$10^3\varepsilon$	$\lambda_{max.}$ (Å)	$10^3\varepsilon$
				Aldehydes (I)				
1	3220	30·5						
2	3520	42·0	2490	10·8				
3	3820	52·0	2720	8·0				
4	4030	61·5	2920	10·6				
5	4250	68·7	3120	9·8	2580	10·3		
6	4400	78·0	3310	9·3	2830	10·4	2590	11·1
7	4570	90·2	3510	9·9	3040	11·6	2750	12·3
				Alcohols (VI)				
3 †	3410 *	46	3290	57	3170 *	47		
4	3710 *	53	3570	68·5	3420 *	54		
5	4020	87	3810	104	3640	71·5		

* Inflexion. † In ethanol.

illustrated in Fig. 1, chloroform being used as solvent. Unlike the simple polyenes, the mono- or di-phenylpolyenes, or even compounds containing the *p*-methoxyphenyl-polyene system, *e.g.*, the alcohols (VI), the *p*-methoxyphenyl-polyene aldehydes show broad, rounded absorption maxima without discernible vibrational fine-structure. In this they resemble merocyanines and cyanines [3,4] (*e.g.*, III and IV). However, as Fig. 2 indicates, $\lambda_{max.}$ is approximately proportional to $n^{\frac{1}{2}}$; in this, series (I) has affinities with the simple polyenes, rather than with the cyanines or merocyanines.[2] Although the flatness of the maxima makes precise location impossible, it appears that series (I) deviates slightly from the Lewis–Calvin relationship for polyenes [2] at large values of n, as the simple polyenes probably do also.* The coefficient k, in the equation $\lambda^2 = kn$, is about 1·9, as compared with values of 2·0 and 2·3 for diphenyl- [16] and dimethyl-polyenes,[12] respectively.

* The data published for the higher dimethylpolyenes ($n > 7$) in Part III,[13] however, overstate this deviation; Bohlmann and Mannhardt [13] have recently prepared the pure all-*trans*-isomers of $CH_3·[CH{=}CH]_n·CH_3$, where $n = 8$, 9, and 10, and observed absorption at appreciably longer wavelengths. Our spectra, and that for $CH_3·[CH{=}CH]_9·CH_3$ published by Bohlmann,[14] must be attributed to mixtures of *cis*-isomers, the all-*trans*-forms having been eliminated by their insolubility. Similar considerations probably apply to the spectra recorded by R. Kuhn [15] for the hydrocarbons $Ph·[CH{=}CH]_n·Ph$, where $n = 11$ and 15.

[13] Nayler and Whiting, *J.*, 1955, 3037.
[13] Bohlmann and Mannhardt, *Chem. Ber.*, 1956, **89**, 1307.
[14] Bohlmann, *Chem. Ber.*, 1952, **85**, 386.
[15] R. Kuhn, *Angew. Chem.*, 1937, **50**, 703.
[16] Hausser, R. Kuhn, and Smakula, *Z. phys. Chem.*, 1935, **29**, 384.

Oscillator strength values for the aldehydes (I) were calculated, by using the equation [17]

$$f = 4{\cdot}31 \times 10^{-9} \int \epsilon d\bar{\nu}$$

with integration between the extrapolated point of zero absorption on the long wavelength side, and the longest-wavelength minimum of the plot of ϵ against $\bar{\nu}$. [This is a somewhat

FIG. 1.

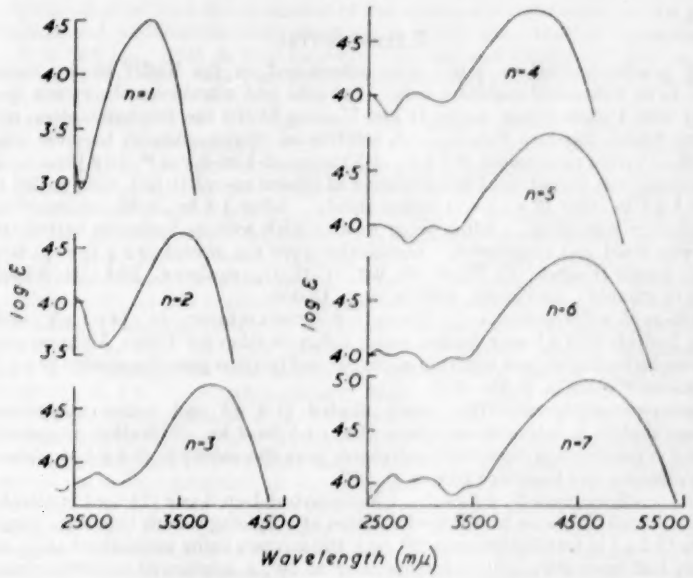


FIG. 2.

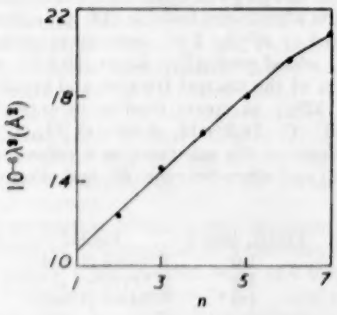
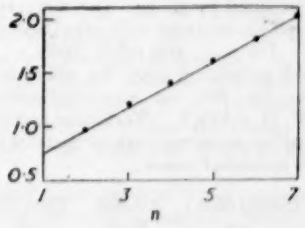


FIG. 3.



arbitrary procedure, but it should be consistent within series (I); in the case of (I; $n = 7$) inclusion of the region between 40,000 and 28,300 cm.$^{-1}$ would increase the value of f by about 0·5.] Fig. 3 illustrates the results; it is clear that a linear relation between n and f exists. The only previous attempt to show such a relation, the work of Hausser, Kuhn, and Smakula [16] on the diphenylpolyenes, was much less successful because of the experimental scatter of the points. A linear relationship for f values is required by Braude's "chromophore areas" theory,[18] which in its simplest form further requires that the

[17] Maccoll, *Quart. Rev.*, 1947, **1**, 16.
[18] Braude, *J.*, 1950, 379.

increment per ·CH:CH· grouping should not vary between one series and another. In Part III,[12] however, the dimethylpolyenes were shown to have oscillator strengths which increased from the triene to the hexaene according to a roughly linear law, but with an increment per ·CH:CH· grouping of approximately 0·5, as against about 0·21 (increased to *ca.* 0·27 when absorption down to 40,000 cm.$^{-1}$ is included) in the present series (I). The early value [16] for the diphenylpolyenes is of the order of 0·22. Evaluation of these results must clearly await more information.

Experimental

Melting points denoted m. p.(K) were determined on the Kofler block; those denoted m. p.(cap.) in an evacuated capilliary tube. Infrared and ultraviolet absorption spectra were determined with Perkin–Elmer model 21 and Unicam SP500 spectrophotometers, respectively.

6-Ethoxy-2-methylhex-5-en-3-yn-2-ol.—A solution of ethylmagnesium bromide was prepared in ether (80 c.c.) from magnesium (2·7 g.). 1-Ethoxybut-1-en-3-yne [20] (10 g.) was added slowly, and the mixture was stirred until the evolution of ethane ceased (1 hr.), then cooled to 0° while acetone (5·8 g.) in ether (5 c.c.) was added slowly. After 1·5 hr., cold, saturated ammonium chloride solution was added. After being washed with sodium hydrogen carbonate solution, the ether was dried and evaporated. Distillation gave the *alcohol* (9·2 g.), b. p. 80°/0·5 mm., n_D^{19} 1·4926—1·4948 (Found: C, 70·15; H, 9·2. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%). Light absorption in ethanol: maximum, 2390 Å; ε = 16,000.

3-p-Methoxyphenylprop-2-en-1-ol.—Methyl *p*-methoxycinnamate (4·0 g.) and lithium aluminium hydride (0·6 g.) were heated under reflux in ether for 1 hr. Addition of water and then aqueous tartaric acid, and isolation of the neutral fraction gave the alcohol (3·4 g.), m. p.(K) 76—79° (Karrer [19] gives m. p. 79—80°).

p-Methoxycinnamaldehyde.—The above alcohol (1·0 g.) and active manganese dioxide (8·2 g.) were shaken in tetrachloroethylene (100 c.c.) for 2 hr. Filtration, evaporation of the solvent, and crystallisation from light petroleum gave the aldehyde (0·9 g.) as plates, m. p.(K) 59—60° (Vorländer and Gieseler [7] give m. p. 58°).

5-p-Methoxyphenylpenta-2 : 4-dienal.—1-Methoxybut-1-en-3-yne (14·6 g.) in tetrahydrofuran (20 c.c.) was added dropwise to a stirred solution of ethylmagnesium bromide, prepared from magnesium (3·2 g.) in tetrahydrofuran (90 c.c.), the mixture being maintained at *ca.* 40°. After the mixture had been stirred for a further hour at 20°, a solution of *p*-methoxybenzaldehyde (18·1 g.) in tetrahydrofuran (20 c.c.) was added dropwise, with external ice cooling, during 20 min. After being stirred for a further 2 hr. at 20° the mixture was again cooled to 0° and treated with ethanol (5 c.c.), then after 20 min. with lithium aluminium hydride (4·0 g.), added during 45 min. in small portions. The mixture was stirred at 20° for 3 hr., once more cooled in ice, and treated successively with ethyl acetate (6 c.c.; added gradually), water (30 c.c.), sulphuric acid (4N; 150 c.c.), and ether (200 c.c.). Isolation of the neutral fraction and crystallisation from light petroleum gave the *aldehyde* (13·1 g., 52%), as cream needles, m. p.(K) 76—78°, raised to 79—80° on recrystallisation (Found: C, 76·5; H, 6·65. $C_{12}H_{12}O_2$ requires C, 76·55; H, 6·45%). (Vorländer and Gieseler [7] describe this substance as a yellow oil.)

Analogous reactions were carried out in ether (*A*) and ether–benzene (*B*), and other reactants varied as indicated below:

Solv.	$LiAlH_4$ (mol.)	Alcohol	Yield (%)	Solv.	$LiAlH_4$ (mol.)	Alcohol	Yield (%)
A	1·0	None	25	*A*	1·0	Ethanol (1 mol.)	27
A	1·5	None	18	*A*	1·0	β-Naphthol (1 mol.)	20
B	1·0	None	17	*A*	1·0 *	Ethanol (1 mol.)	15
B	0·5	None	3				

* Refluxed for 1 hr.

5-Phenylpenta-2 : 4-dienal.—The method described above being used, benzaldehyde (26·5 g.) in tetrahydrofuran (40 c.c.) was added to a solution of the Grignard reagent prepared from magnesium (7·5 g.) and methoxybutenyne (27·3 g.) in tetrahydrofuran (175 c.c.). After 1·5 hr. at 20°, ethanol (11·5 c.c.) and lithium aluminium hydride (9·5 g.) were added at 0°, and the mixture was stirred for 18 hr. at 20°. Distillation of the neutral fraction gave a liquid (32 g.),

[19] Karrer, *Helv. Chim. Acta*, 1928, **11**, 1209.
[20] Johnson, *J.*, 1946, 1009.

b. p. 102—104°, which solidified. Crystallisation gave the *aldehyde* (30 g.) as thick needles, m. p. (K) 42—43°. (Kethur, Klein, and Wietbrock [8] give m. p. 38—39°.)

Dodeca-2 : 4 : 6 : 8 : 10-pentaenal [with P. NAYLER].—A solution of the Grignard reagent from magnesium (6·6 g.), ethyl bromide, and methoxybutenyne (20 g.) was prepared in tetrahydrofuran (170 c.c.). A solution of octa-2 : 4 : 6-trienal (30 g.) in tetrahydrofuran (150 c.c.) was added slowly, without cooling; after 1·5 hr. at 20°, alcohol (13·5 c.c.) and solid lithium aluminium hydride (9·3 g.) were added successively, with stirring. After 1 hr. water was added, followed by saturated aqueous tartaric acid, and the neutral fraction was isolated with ether. Evaporation of solvent and treatment of the residue with cold ether left 8·6 g. of crude aldehyde undissolved, yielding the aldehyde (8 g.), m. p. (K) 160—163°, on crystallisation from methanol; this had $\lambda_{max.}$ 3850 Å in chloroform (Schmitt and Obermeit [21] give m. p. 165°). A further 5 g. (m. p. 161—164°) was obtained by treatment of the ether-soluble fraction with 80% methanol.

7-p-*Methoxyphenylhepta-2 : 4 : 6-trienal*.—By the same general method, *p*-methoxycinnamaldehyde (12·6 g.) in tetrahydrofuran (30 c.c.) was treated with the Grignard reagent from magnesium (2·55 g.) and methoxybutenyne (10·8 g.) in tetrahydrofuran, then with lithium aluminium hydride overnight at 20°. Decomposition of the complex and addition of ether precipitated part of the product (4·5 g.), and crystallisation of the neutral fraction yielded a further 3·1 of the *aldehyde*, which separated from benzene–light petroleum as lemon-yellow needles, m. p.(K) 134·5—135·5° (Found : C, 78·4; H, 6·7. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

9-p-*Methoxyphenylnona-2 : 4 : 6 : 8-tetraenal*.—5-*p*-Methoxyphenylpenta-2 : 4-dienal (22·8 g.) in tetrahydrofuran (50 c.c.) was similarly condensed with the Grignard reagent from magnesium (3·84 g.) and methoxybutenyne (16·4 g.). Addition of ethanol and lithium aluminium hydride, decomposition, and addition of ether precipitated the product almost completely; after crystallisation from benzene the *tetraenal* formed golden-yellow needles, m. p.(K) 178—179° (Found : C, 79·75; H, 6·8. $C_{16}H_{16}O_2$ requires C, 79·95; H, 6·7%).

1-*Methoxy*-11-p-*methoxyundeca-1 : 6 : 8 : 10-tetraen-3-yn-5-ol* (V; $n = 3$).—By the above procedure 7-*p*-methoxyphenylhepta-2 : 4 : 6-trienal (4·25 g.) in tetrahydrofuran (60 c.c.) was condensed with the Grignard reagent from magnesium (1 g.) and methoxybutenyne (4·6 g.) in tetrahydrofuran (40 c.c.). Addition of concentrated aqueous ammonium nitrate solution (75 c.c.) and ether (75 c.c.) with agitation and ice-cooling gave an organic extract which was washed with potassium hydrogen carbonate solution, dried, and evaporated at 20° under reduced pressure. Crystallisation of the residue from benzene–light petroleum gave the desired *alcohol* (4·37 g., 74%), as a cream powder, m. p. (K) 112—120° (decomp.) (Found : C, 76·75; H, 6·8. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

11-p-*Methoxyphenylundeca-2 : 4 : 6 : 8 : 10-pentaen-1-al*.—(*a*) The foregoing alcohol (4·37 g.) in ethyl acetate (350 c.c.) was shaken in hydrogen in the presence of a partially poisoned palladium catalyst [9] (210 mg.) and quinoline (135 mg.) until 0·94 mol. of hydrogen had been absorbed. Uptake then ceased. After filtration, tetrahydrofuran (30 c.c.) and saturated aqueous oxalic acid (20 c.c.) were added; the mixture slowly deposited crystals. After being set aside overnight at 20° the *aldehyde* (2·7 g., 51% overall) formed pale orange leaflets or laths, m. p.(cap.) 202—203° (Found : C, 80·9; H, 6·95. $C_{18}H_{18}O_2$ requires C, 81·15; H, 6·8%).

(*b*) If reduction was effected *in situ* with lithium aluminium hydride, the trienal (1·86 g.) gave the pentaenal (50 mg., 2%), m. p.(cap.) 202—203°, when ether was added to the tetrahydrofuran solution.

Since completion of this work, Wizinger and Kölliker have reported [22] the preparation of this aldehyde by condensation of *p*-methoxybenzaldehyde and crotonaldehyde. Their product was isolated by crystallisation only, and must inevitably have contained hexadecaheptaenal, etc., and the aldehydes (I; $n = 7, 9, \ldots$.) in minor quantities; they report it as scarlet crystals, m. p. 198·5—200°, $\lambda_{max.}$ 4220 Å (in alcohol). Our specimen had $\lambda_{max.}$ 4165 Å in this solvent.

1-*Methoxy*-13-p-*methoxyphenyltrideca-1 : 6 : 8 : 10 : 12-pentaen-3-yn-5-ol* (V; $n = 4$).—Addition of a solution of 9-*p*-methoxyphenylnona-2 : 4 : 6 : 8-tetraenal (7·5 g.) in warm tetrahydrofuran (400 c.c.) to one of the Grignard reagent from magnesium (2·25 g.) and methoxybutenyne (10·2 g.) in tetrahydrofuran (115 c.c.), and isolation of the product as above gave the *alcohol* (6·05 g., 60%) as a cream powder, m. p.(K) 138—142° (decomp.) (Found : C, 78·05; H, 6·85. $C_{21}H_{22}O_3$ requires C, 78·25; H, 6·9%).

13-p-*Methoxyphenylpentadeca-2 : 4 : 6 : 8 : 10 : 12-hexaenal*.—The above alcohol (6·05 g.) in

[21] Schmitt and Obermeit, *Annalen*, 1941, **547**, 285.
[22] Wizinger and Kölliker, *Helv. Chim. Acta*, 1955, **38**, 372.

ethyl acetate (520 c.c.) was shaken in hydrogen in the presence of lead-poisoned palladium [*] (280 mg.) and quinoline (180 mg.) until 1·1 mol. had been absorbed. Filtration and addition of tetrahydrofuran (80 c.c.) and saturated aqueous oxalic acid resulted in the slow separation of the *aldehyde* (3·13 g., 34% overall), which formed scarlet prisms, m. p. 230—231° (decomp.), after crystallisation from xylene.

1-*Methoxy*-15-p-*methoxyphenylpentadeca*-1 : 6 : 8 : 10 : 12 : 14-*hexaen*-3-*yn*-5-*ol* (V; $n = 5$).—A suspension of 11-*p*-methoxyphenylundeca-2 : 4 : 6 : 8 : 10-pentaenal (500 mg.) in tetrahydrofuran (40 c.c.) was added to a solution of the Grignard reagent prepared from magnesium (140 mg.) and 1-methoxybutenyne (620 mg.) in tetrahydrofuran. A homogeneous solution resulted, and after 2 hr. the complex was decomposed and the neutral fraction isolated. Crystallisation from acetone–light petroleum gave a pale yellow *alcohol* (450 mg., 70%), m. p.(cap.) 148° (decomp.) (Found : C, 79·4; H, 7·0. $C_{33}H_{24}O_3$ requires C, 79·3; H, 6·95%).

15-p-*Methoxyphenylpentadeca*-2 : 4 : 6 : 8 : 10 : 12 : 14-*heptaenal*.—The above alcohol (200 mg.) in ethyl acetate (70 c.c.) was shaken in hydrogen in the presence of the palladium–lead catalyst (10 mg.) and quinoline (6 mg.); absorption apparently ceased after the uptake of 0·25 mol. Hydrolysis to the aldehyde as described above and crystallisation from pyridine gave the *aldehyde* (30 mg., 13% overall) as purple-red microscopic prisms, m. p.(cap.) 240—241° (decomp.) (Found : C, 82·25; H, 7·2. $C_{33}H_{22}O_3$ requires C, 83·0; H, 6·95%).

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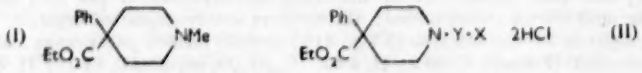
788. *Some New Analogues of Pethidine.* Part I.*†

By R. J. ANDERSON, P. M. FREARSON, and E. S. STERN.

Substituted ethyl 1-alkyl-4-phenylpiperidine-4-carboxylates in which the alkyl group carries a nitrogenous heterocyclic residue have been prepared from ethyl 4-phenylpiperidine-4-carboxylate for pharmacological test as analgesics.

THE discovery of the analgesic properties of pethidine (I) was followed by the synthesis and pharmacological evaluation of a large number of related substances. Pethidine, although not very potent on a weight basis, has held its place as the most widely used synthetic analgesic because of its low toxicity. In the present work, further analogues of pethidine have been synthesised in the hope that more potent substances retaining the low toxicity of pethidine might be obtained.



The substances synthesised have the general formula (II), in which Y represents an alkyl group carrying a heterocyclic residue (X) (cf. Table); the two heterocyclic systems in each case are linked through their nitrogen atoms by a two (or three) carbon-atom chain (Y). Although two derivatives of pethidine carrying a basic substituent at the nitrogen atom have been reported,[1] none has been described hitherto in which the 1-alkyl group was substituted by a heterocyclic residue.

The starting material for the syntheses reported here was ethyl 4-phenylpiperidine-4-carboxylate,[2] an intermediate in one of the commercial methods [3] of making pethidine. One of two methods was used for the preparation of the desired substituted substances: preferably the secondary base (I; H in place of Me) was treated with the desired substituted alkyl halide, but in the cases where difficulties might have arisen (Nos. 4, 7, 8, and 9 in Table) the

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† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Schaumann, *Arch. Path. Pharmakol.*, 1940, **196**, 127.
[2] Eisleb, *Ber.*, 1941, **74**, 1433; cf. Walton, B.P. 592,016.
[3] B.I.O.S. Final Report No. 766, p. 60 *et seq.*

secondary base was first alkylated with ethylene chlorohydrin; the resulting 1-hydroxyethyl compound was converted into the chloroethyl compound which reacted readily with the heterocyclic bases chosen. The desired products were isolated and characterised as hydrochlorides.

The substances prepared were submitted to pharmacological tests, the results of which have been reported.[4] When this work was in progress (1954—55), it was generally accepted [5] that replacement of the *N*-methyl group of pethidine by other groups decreased or abolished analgesic activity. It was surprising therefore, that four of the substances, namely, Nos. 3, 5, 10, and 11 in the Table, had very considerable analgesic potency; ethyl

Pethidine analogues (II).

No.	Y	X	M. p. (decomp.)
1	$CH_2 \cdot CH_2$	Pyrrolidino	259—262°
2	$CH_2 \cdot CH_2$	Piperidino	270—272
3	$CH_2 \cdot CH_2$	Morpholino	264—266
4	$CH_2 \cdot CH_2$	Piperazino	244—246
5	$CH_2 \cdot CH_2$	Tetrahydro-1 : 4-thiazin-4-yl	266
6	$CH_2 \cdot CH_2$	4-Ethoxycarbonyl-4-phenylpiperidino	241—243
7	$CH_2 \cdot CH_2$	4-Methylpiperidino	270—272
8	$CH_2 \cdot CH_2$	1 : 2 : 3 : 6-Tetrahydropyridino	257—259
9	$CH_2 \cdot CH_2$	4-Hydroxypiperidino	250—252
10	$CH_2 \cdot CH_2 \cdot CH_2$	Morpholino	240
11	$CHMe \cdot CH_2$	Morpholino	235—237

		Found (%)				Required (%)			
No.	Formula	C	H	N	Cl	C	H	N	Cl
1	$C_{20}H_{32}O_2N_2Cl_2$	59·0	8·0	7·15	17·65	59·5	7·9	6·95	17·6
2	$C_{20}H_{34}O_2N_2Cl_2$	59·7	7·6	6·75	17·2	60·4	8·2	6·7	17·0
3	$C_{20}H_{32}O_3N_2Cl_2$	56·9	7·65	6·65	16·9	57·3	7·7	6·7	16·9
4	$C_{20}H_{33}O_2N_3Cl_2$	53·0	7·6	—	—	52·9	7·5	—	—
5	$C_{20}H_{32}O_2N_2SCl_2$	55·6	7·55	6·35	—	55·15	7·4	6·45	—
6	$C_{30}H_{42}O_4N_2Cl_2$	62·9	7·35	4·75	12·5	63·7	7·4	4·95	12·55
7	$C_{22}H_{36}O_2N_2Cl_2$	61·25	7·9	6·3	—	61·2	8·4	6·5	—
8	$C_{21}H_{32}O_2N_2Cl_2$	59·9	7·35	6·75	—	60·7	7·7	6·75	—
9	$C_{21}H_{34}O_3N_2Cl_2$	58·0	7·8	6·15	—	58·2	7·9	6·45	—
10	$C_{21}H_{34}O_3N_2Cl_2$	57·9	7·9	6·4	15·9	58·2	7·9	6·45	16·3
11	$C_{21}H_{34}O_3N_2Cl_2$	57·7	7·9	6·8	16·0	58·2	7·9	6·45	16·3

1-2′-morpholinoethyl-4-phenylpiperidine-4-carboxylate, in particular, was 3—7 times as potent as pethidine. These appeared to be the first known cases of potent analgesics carrying a large substituent at the "piperidine" nitrogen, though one further closely related example, phenethylnorpethidine, has lately been reported.[6]

It was particularly striking that the four highly active pethidine analogues of this series contained the morpholine or tetrahydro-1 : 4-thiazine ring system. This led to the synthesis, by simple new routes (cf. Experimental section), of two known morpholine derivatives, 1 : 2-dimorpholinoethane and 2-morpholinoethyl*cyclo*hexane, and of the new *N*-(2-4′-hydroxypiperidinoethyl)morpholine; these substances were devoid of analgesic activity. The conclusion was reached, therefore, that whilst analgesic activity did not reside in the morpholine moiety of the molecule itself, the morpholine ring system had an important bearing on analgesic potency in this series of pethidine analogues. Further work is in progress.

Experimental

Intermediates.—The intermediate alkyl halides were prepared by recorded methods. 2-Pyrrolidinoethyl chloride hydrochloride had m. p. 172—173° (Wright *et al.*[7] give m. p. 173·5—174°); 2-piperidinoethyl chloride hydrochloride had m. p. 228° (Dunlop [8] gives m. p. 231°, but Marckwald and Frobenius [9] give m. p. 208°); 2-morpholinoethyl chloride hydrochloride had

[4] Millar and Stephenson, *Brit. J. Pharmacol.*, 1956, **11**, 27; Green and Ward, *ibid.*, p. 32.
[5] Cf. Burger, "Medicinal Chemistry," p. 174 Interscience, New York, 1951; Braenden, Eddy, and Halbach, *Bull. Wld. Hlth. Org.*, 1955, **13**, 937.
[6] Perrine and Eddy, *J. Org. Chem.*, 1956, **21**, 125.
[7] Wright, Kolloff, and Hunter, *J. Amer. Chem. Soc.*, 1948, **70**, 3098.
[8] Dunlop, *J.*, 1912, **101**, 1998.
[9] Marckwald and Frobenius, *Ber.*, 1901, **34**, 3556.

m. p. 182° (Mason and Block [10] give m. p. 182—182·5°); 2-(tetrahydro-1 : 4-thiazin-1-yl)ethyl chloride hydrochloride had m. p. 208° (Gilman and Woods [11] give m. p. 206—208°); 3-morpholinopropyl chloride hydrochloride had m. p. 168° (Adams and Whitmore [12] give m. p. 168—170°); and 1-methyl-2-morpholinoethyl chloride hydrochloride had m. p. 176—177° (Attenburrow *et al.*[13] give m. p. 176—178°).

Ethyl 1-2′-*Chloroethyl*-4-*phenylpiperidine*-4-*carboxylate* (I; R = ·CH_2·CH_2·Cl).—Ethyl 4-phenylpiperidine-4-carboxylate (20 g.), m. p. *ca.* 33°, b. p. 150°/1·8 mm. (cf. Eisleb [2]) [*hydrobromide*, m. p. 165—166° (Found: N, 4·55; Br, 25·4. $C_{14}H_{20}O_2NBr$ requires N, 4·45; Br, 25·45%)], and ethylene chlorohydrin (6 ml.) were refluxed in ethyl acetate for 2·5 hr. For isolation of the intermediate (II; YX = ·CH_2·CH_2·OH), the ethyl acetate was removed and the liquid remaining distilled. Ethyl 1-2′-hydroxyethyl-4-phenylpiperidine-4-carboxylate (mentioned, but not described by Schaumann [1]) has b. p. 125—128°/1—1·5 mm., n_D^{19} 1·5215 (Found: C, 70·1; H, 8·6; N, 4·75. Calc. for $C_{16}H_{23}O_3N$: C, 69·3; H, 8·35; N, 5·05%).

To prepare the product (II; YX = ·CH_2·CH_2Cl), the stirred cool mixture was slowly treated with thionyl chloride (8 ml.) and, when addition was complete, the solution was boiled for a short time until crystallisation started. The *hydrochloride* of 1-2′-chloroethyl-4-phenylpiperidine-4-carboxylate was collected, and recrystallised from aqueous alcohol. When pure it (*ca.* 8·5 g.) had m. p. 219—220° (decomp.) (Found: C, 58·4; H, 6·9; N, 4·05; Cl, 21·4. $C_{16}H_{22}O_2NCl,HCl$ requires C, 57·8; H, 6·9; N, 4·2; Cl, 21·4%).

Preparation of Tertiary Bases.—(A) *Ethyl* 1-2′-*morpholinoethyl*-4-*phenylpiperidine*-4-*carboxylate*. Ethyl 4-phenylpiperidine-4-carboxylate (7 g.), 2-morpholinoethyl chloride (4·5 g.), and anhydrous sodium carbonate (1·8 g.) were boiled in alcohol (50 ml.) for several hours. The suspension was filtered and the filtrate concentrated under reduced pressure. Ethanolic hydrogen chloride was then added to precipitate the crude product; recrystallisation from aqueous ethanol gave the pure dihydrochloride (cf. Table) (9·8 g.), m. p. 264—266° (decomp.). *Ethyl* 1-2′-*morpholinoethyl*-4-*phenylpiperidine*-4-*carboxylate*, regenerated from the dihydrochloride, had b. p. 188—192°/0·5 mm., n_D^{18} 1·5276 (Found: C, 69·4; H, 8·85; N, 8·45. $C_{20}H_{30}O_3N_2$ requires C, 69·3; H, 8·75; N, 8·1%), and gave a *picrate*, m. p. 247—248° (decomp.) (Found: N, 14·25. $C_{20}H_{30}O_3N_2,2C_6H_3O_7N_3$ requires N, 13·9%).

(B) *Ethyl* 1-2′-*piperazinoethyl*-4-*phenylpiperidine*-4-*carboxylate*. Ethyl 1-2′-chloroethyl-4-phenylpiperidine-4-carboxylate hydrochloride (5·5 g.) (see above) in alcohol was neutralised with alcoholic sodium ethoxide (1 equiv.); piperazine (3·6 g.) was added and the mixture boiled for 4 hr. After concentration under reduced pressure, addition of alcoholic hydrogen chloride gave the desired trihydrochloride, which was recrystallised from aqueous alcohol and then had m. p. 244—246° (decomp.).

1 : 2-*Dimorpholinoethane*.—Morpholine (10 g.) and 2-morpholinoethyl chloride (17 g.) were boiled for 1 hr.; two layers were formed. To the mixture was added an excess of aqueous ammonia, and the organic bases were extracted into chloroform. Vacuum-distillation gave, besides unchanged morpholinoethyl chloride (4·5 g.), b. p. 90°/12 mm., the desired 1 : 2-dimorpholinoethane (12 g.), b. p. 140—150°/12 mm., m. p. 70—72° (Knorr and Brownsden [14] give m. p. 74°, b. p. 153—154°/9 mm.).

2′-*Morpholinoethyl*cyclo*hexane*.—The decarboxylated condensation product (76 g.), b. p. 97—99°/15 mm. (cf. Cope *et al.*[15]), of cyanoacetic acid and *cyclo*hexanone on hydrogenation over Raney nickel in alcoholic ammonia at 55—60°/100 atm. for 24 hr. gave 2′-aminoethyl*cyclo*hexane (63 g.), b. p. 70°/15 mm., 188°/1 atm., n_D^{17} 1·4720 (Wallach [16] gives b. p. 188—189°, n_D^{19} 1·4647). This amine (30 g.) and di-(2-chloroethyl) ether (34 g.) in boiling ethanol (100 ml.) over sodium carbonate (25 g.) for 8 hr. yielded, besides much unchanged starting material, 2′-morpholinoethyl*cyclo*hexane (12 g.), b. p. 130°/12 mm., which gave a hydrochloride, m. p. 253—254° (Blicke and Zienty [17] give b. p. 132—134°/12 mm.; hydrochloride, m. p. 260—261°).

4-(2-4′-*Hydroxypiperidinoethyl*)*morpholine*.—4-Hydroxypiperidine (24·7 g.), b. p. 110—125°/10—15 mm. (Bowden and Green [18] give b. p. 110—115°/10 mm.), and 2-morpholinoethyl chloride (37 g.) were boiled in alcohol (150 ml.) over sodium carbonate (13 g.) for several hours.

[10] Mason and Block, *J. Amer. Chem. Soc.*, 1940, **62**, 1443.
[11] Gilman and Woods, *ibid.*, 1945, **67**, 1843.
[12] Adams and Whitmore, *ibid.*, p. 735.
[13] Attenburrow, Elks, Hems, and Speyer, *J.*, 1949, 510.
[14] Knorr and Brownsden, *Ber.*, 1902, **35**, 4472.
[15] Cope, D'Addieco, Whyte, and Glickman, *Org. Synth.*, 1951, **31**, 25.
[16] Wallach, *Annalen*, 1907, **353**, 284; 1908, **359**, 311.
[17] Blicke and Zienty, *J. Amer. Chem. Soc.*, 1939, **61**, 771.
[18] Bowden and Green, *J.*, 1952, 1164.

The suspension was filtered, the filtrate concentrated, and 20% alcoholic hydrogen chloride added: 4-(2-4′-*hydroxypiperidinoethyl*)*morpholine dihydrochloride* separated; on crystallisation from aqueous alcohol it (50 g.) had m. p. 295° (decomp.) (Found: C, 46·35; H, 8·45; N, 9·55; Cl, 24·3. $C_{11}H_{22}O_2N_2,2HCl$ requires C, 46·0; H, 8·4; N, 9·75; Cl, 24·7%). Regeneration with aqueous alkali, extraction into chloroform, and distillation gave the *base*, b. p. 155—158°/2—3 mm., which crystallised rapidly on cooling and, after recrystallisation from ether–light petroleum, had m. p. 65—66° (Found: C, 61·6; H, 10·1; N, 13·1. $C_{11}H_{22}O_2N_2$ requires C, 61·65; H, 10·35; and N, 13·05%).

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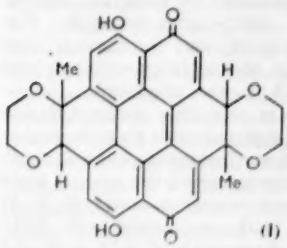
789. *Colouring Matters of the Aphididæ. Part XV.* The Alkaline Inversion of Erythroaphin-sl and its Derivatives.*†

By A. W. JOHNSON, SIR ALEXANDER R. TODD, and J. C. WATKINS.

Solvent systems are described for the paper chromatographic analysis of mixtures of aphin pigments and particularly for the differentiation of *fb* and *sl* isomers. Silica columns have been used for larger-scale separations. Erythroaphin-*fb* has been isolated from the products of reaction of alkali with erythroaphin-*sl*, and hydroxyerythroaphin-*fb* from the reaction of erythroaphin-*sl* with sodium periodate.

IN an earlier paper [1] structure (I) was advanced for erythroaphin, the relatively stable, deep red aphin pigment. Two isomers of erythroaphin have been obtained from the protoaphins of different aphid species, the glucosidic water-soluble protoaphins being converted successively into xanthoaphins, chrysoaphins, and erythroaphins. The difference between these two isomers, erythroaphin-*fb* and erythroaphin-*sl*, has been shown to be stereochemical on the grounds of the close similarity of chemical and light-absorption properties and the methods by which erythroaphin-*sl* can be converted into the -*fb* isomer. Amination or hydroxylation of erythroaphin-*sl* gave the diamino- or dihydroxy-derivative of erythroaphin-*fb*, and reduction of these substitution products with zinc and acetic acid yielded erythroaphin-*fb* itself.[2] Ultraviolet irradiation of either tetra-acetyldihydro-erythroaphin-*fb* or -*sl* caused racemisation and an equilibrium mixture was obtained containing the two isomers together with a third isomer derived from an erythroaphin which has not, as yet, been obtained from aphid species.[3] It was deduced that the ring junctions between the two sets of non-aromatic rings were *cis-cis* for erythroaphin-*fb*, *cis-trans* for erythroaphin-*sl*, and that the new artificially produced erythroaphin was the *trans-trans*-isomer. The arguments leading to these conclusions depended on the quantitative determination of acetaldehyde liberated from the erythroaphin-*fb* and -*sl* on treatment with strong acids, as well as stereochemical considerations of the course of the addition reactions.



(I)

Direct conversion of the less stable erythroaphin-*sl* into the -*fb* isomer by the action of alkali has not hitherto been accomplished, partly because of the difficulty of recognising small quantities of one isomer in the presence of the others and partly because of the ready nuclear hydroxylation which occurs in alkaline solution. Solvent systems have now been

* Part XIV, *J.*, 1955, 1144.
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Brown, Calderbank, Johnson, Joshi, Quayle, and Todd, *J.*, 1955, 959.
[2] Brown, Calderbank, Johnson, MacDonald, Quayle, and Todd, *J.*, 1955, 954.
[3] Brown, Calderbank, Johnson, Quayle, and Todd, *J.*, 1955, 1144.

discovered which permit the analysis of such reaction products by chromatography on paper; and, for larger quantities, columns of silica, deactivated by the addition of small amounts of water, have been used successfully. It has thus been found that the action of hot 0·5% aqueous sodium hydroxide on erythroaphin-*sl* is complex and gives in the course of 30 minutes at least five products; however, crystalline erythroaphin-*fb* has been isolated in about 10% yield from the mixture. Apart from insoluble black materials, the other compounds formed appeared to be mono- and di-hydroxy-derivatives of erythroaphin.

A similar experiment with erythroaphin-*fb* was superficially the same but none of the -*sl* isomer was found among the products. The ease with which the inversion of erythroaphin-*sl* and its derivatives occurred is emphasised by the formation of hydroxyerythroaphin-*fb* as well as the -*sl* isomer when an aqueous-dioxan solution of erythroaphin-*sl* is heated under reflux for 30 hours. Pure hydroxyerythroaphin-*fb* was also obtained by heating erythroaphin-*sl* with a dilute solution of sodium periodate. Paper-chromatographic evidence has also been obtained for the formation of erythroaphin-*fb* from erythroaphin-*sl* by the action of hot dilute sulphuric acid.

Cyclic compounds containing an activated hydrogen atom at a ring junction are known to be converted into the more stable isomers by alkali or acids, and examples are common among steroids[4] and related compounds;[5] the direct conversion of erythroaphin-*sl* into erythroaphin-*fb* is most readily explained by this type of mechanism. In Part XIV of this series the interconversion of erythroaphin derivatives was discussed. At the time that paper was written we had no examples of conversion from the *sl* into the *fb* series, in which the reactions involved did not include reduction and reoxidation accompanied by the introduction of at least two substituents. Consequently the explanations suggested were based largely on considerations of steric hindrance. The results recorded in the present memoir show that direct conversion of erythroaphin-*sl* into erythroaphin-*fb* can be effected by treatment with alkali, or, less readily, acid. This being so, steric hindrance, although it may be a factor in some reactions, is much less important than was suggested in Part XIV and may indeed be of minor significance. Basic reagents bring about inversion rapidly and it is therefore almost certain that inversion occurs with the introduction of the first amino- or hydroxy-group during formation of diamino- and dihydroxy-erythroaphins. Inversion with acid is much slower than with alkali, a fact which is of itself sufficient to explain the apparent lack of inversion during the Thiele acetylation and bromination of erythroaphin-*sl*.

Experimental

Chromatography of the Aphin Pigments.—Best results were obtained by using the organic layers of "AnalaR" chloroform–light petroleum (b. p. 100—120°)–water mixtures. For general use these solvents were used in the proportion 2 : 2 : 1 respectively; for xanthoaphins and chrysoaphins the proportion 4 : 1 : 1 was preferred; for the hydroxy-erythroaphins 10 : 5 : 3, and for the fast-moving erythroaphins the ratio 3 : 7 : 2, was employed. Reproducible R_F values were obtained with Whatman No. 4 paper in ascending chromatograms when (i) a small tank (30 × 8 cm.) was used, (ii) the solvent was replaced after each chromatogram, (iii) the minimum amount of pigment was used (a spot which was just visible was sufficient) and (iv) each chromatogram was run for approximately 1 hr., during which the solvent front moved 15—18 cm. When the organic layer of the chloroform–petroleum–water (2 : 2 : 1) mixture was used, typical R_F values were: erythroaphin-*sl*, 0·93; erythroaphin-*fb*, 0·78; hydroxyerythroaphin-*sl*, 0·14; hydroxyerythroaphin-*fb*, 0·14; chrysoaphin-*sl*, 0·53, 0·44, and 0·33 (indicating different isomers); chrysoaphin-*fb*, 0·18; xanthoaphin-*sl*, 0·08 and 0·02 (different isomers); and xanthoaphin-*fb*, 0·02. With the same solvent mixture in the ratio 4 : 1 : 1, the following values were obtained: xanthoaphin-*sl*, 0·53 and 0·28; chrysoaphin-*fb*, 0·65; xanthoaphin-*fb*, 0·12. Discussion of isomerism among xanthoaphins and chrysoaphins is deferred until further investigation of its nature is complete. Faint spots were best detected in ultraviolet light.

Chromatography on Silica.—Good results were obtained with silica gel (40-mesh) containing 10% by wt. of water and equilibrated by rolling for 24 hr. The column was packed by using

[4] See, for example, Crawshaw, Henbest, Jones, and Wyland, *J.*, 1955, 3420.
[5] See, for example, Walker, *J.*, 1954, 3960.

1 : 1 benzene–light petroleum (b. p. 60—80°), and a benzene solution of the substance was brought on the column. Elution was effected with benzene and then with benzene–propan-2-ol mixtures. For aphins which are very strongly absorbed, *e.g.*, dihydroxyerythroaphin, the silica–water proportion was raised to 20 : 3, and pressure was sometimes necessary to ensure movement through the column.

Action of Alkali on Erythroaphin-sl.—1% Aqueous sodium hydroxide (200 c.c.) was added to a solution of erythroaphin-*sl* (400 mg.) in dioxan (200 c.c.), and the mixture heated under reflux for ½ hr. The product was cooled and acidified with 3N-hydrochloric acid, and the solution thoroughly extracted with ether; the insoluble black material which formed at the interface was discarded. The ethereal extract was washed and dried, the solvent removed, and the residue dissolved in " AnalaR " benzene (200 c.c.). The benzene solution was chromatographed on silica gel–water (9 : 1; 65 g.), and the following fractions were taken, benzene containing increasing proportions of propan-2-ol being the eluant: (1) benzene containing 0·25% of propan-2-ol (400 c.c.) + benzene containing 0·5% of propan-2-ol (100 c.c.) (70 mg.); (2) benzene containing 0·5% of propan-2-ol (100 c.c.) (1 mg.); (3) benzene containing 0·5% of propanol-2-ol (400 c.c.) + benzene containing 2% of propan-2-ol (100 c.c.) (67 mg.); (4) benzene containing 2% of propan-2-ol (500 c.c.) (46 mg.). Fraction (1) was crystallised from chloroform–ethanol [6] and gave erythroaphin-*fb* (42 mg.) (Found: C, 70·4; H, 4·4. Calc. for $C_{20}H_{22}O_8$: C, 70·6; H, 4·35%). The identity of the product was confirmed by chromatography and determination of its ultraviolet and infrared spectra.[7] No crystalline products were isolated from fraction 3 or 4 but chromatography suggested the presence of hydroxy-derivatives of erythroaphin.

Action of Water on Erythroaphin-sl.—Hot water (50 c.c.) was added to a solution of erythroaphin-*sl* (100 mg.) in freshly purified dioxan (100 c.c.), and the solution heated under reflux for 30 hr. It was then cooled, diluted with an equal a volume of water, and acidified with 3N-hydrochloric acid. The solution was extracted with ether (3 × 150 c.c.) and then chloroform (100 c.c.), and the combined extracts were washed, dried (Na_2SO_4), and evaporated. The residue was dissolved in " AnalaR " benzene (100 c.c.) and chromatographed on silica gel (15 g.; containing 3 parts of water to 20 parts of silica). The following fractions were taken: (i) benzene (100 c.c.) (10 mg.); (ii) benzene (300 c.c.) (40 mg.); (iii) benzene (200 c.c.) (6 mg.); (iv) benzene containing 0·5% of propan-2-ol (300 c.c.) (15 mg.). Each fraction was investigated by paper chromatography: fraction (i) appeared to be essentially unchanged erythroaphin-*sl*, and fraction (ii) a mixture of monohydroxy-derivatives. Fraction (ii) was crystallised from chloroform–ethanol, and the first crop (7 mg.) recrystallised from the same solvent. The crystalline product (3 mg.) was a hydroxyerythroaphin-*sl* which yielded erythroaphin-(*sl*?) after reduction with zinc and acetic acid. The second crop (13 mg.) from the crystallisation, on recrystallisation proved to be a mixture of the isomers of hydroxyerythroaphin (chromatography and infrared spectrum). Reduction with zinc and acetic gave erythroaphin-*fb* containing a small quantity of the -*sl* isomer.

Action of Sodium Periodate on Erythroaphin-sl.—A hot solution of sodium periodate (50 mg.) in water (50 c.c.) was added to a solution of erythroaphin-*sl* (100 mg.) in dioxan (50 c.c.), and the resulting suspension heated under reflux for 6 hr. Dioxan (50 c.c.) was then added to effect complete dissolution and the heating continued for a further 8 hr. The volume of the solution was reduced to 100 c.c., and the mixture heated under reflux for a further 6 hr., after which it was established by chromatography that very little unchanged erythroaphin remained. The product was extracted into benzene as described in the previous experiment and the benzene solution put on a column of silica gel (15 g.; containing water as above) packed with 1 : 1 benzene–light petroleum (b. p. 60—80°). Hydroxyerythroaphin and any unchanged erythroaphin were not absorbed on the column but the dihydroxyerythroaphins were retained and could be eluted with benzene containing 0·5% of propan-2-ol. The hydroxyerythroaphin fraction (40 mg.) was purified by crystallisation from chloroform–ethanol, being obtained as red needles (Found: C, 67·9; H, 4·2. Calc. for $C_{20}H_{22}O_9$: C, 68·4; H, 4·2%). The infrared spectrum and the chromatographic behaviour of the product were identical with those of authentic hydroxyerythroaphin-*fb*. Reduction of the product with zinc and acetic acid [6] gave erythroaphin-*fb* containing a trace only of the -*sl* isomer (chromatography).

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[6] Brown, Johnson, MacDonald, Quayle, and Todd, *J.*, 1952, 4928.
[7] Johnson, Todd, *et al.*, *J.*, 1950, 477; 1951, 2633.

790. *The Alleged Occurrence of Vitamin A in Baker's Yeast.**

By F. W. Heaton, J. S. Lowe, and R. A. Morton.

The claim that vitamin A is produced in yeast after incubation in an atmosphere of oxygen has been tested but not verified. A substance with an absorption maximum at 272 mμ and an inflexion near 330 mμ has, however, been found to occur in yeast in small quantities. This strongly resembles a substance ("SA") hitherto found in animal products only.

Ernster, Zetterström, and Lindberg [1] claimed to have discovered vitamin A in yeast which had been incubated in an atmosphere of oxygen. There does not appear to have been any other claim to have found vitamin A in yeast. In fact it is generally thought that no exception has been proved to the rule that vitamin A itself occurs only in animal tissues, although carotenoid provitamins of course occur widely in plants. The surprising claim of Ernster *et al.*[1] has neither been withdrawn nor refuted and it therefore seemed necessary to repeat the experimental work.

The results recorded below afford no support for the claim that yeast incubated in a stream of oxygen forms vitamin A. Nevertheless they demonstrate that a substance indistinguishable from "SA" can occur in an organism not belonging to the animal kingdom.

Experimental

Our first experiment was carried out according to the directions of the above authors: 1 kg. of baker's yeast (D.C.L.) suspended in distilled water (4 l.) containing glucose (50 g.), ethanol (50 ml.), ammonium sulphate (5 g.), and disodium monohydrogen phosphate (950 mg.) was cultivated in an atmosphere of oxygen produced by bubbling oxygen vigorously through the suspension. The temperature was maintained at 25—30°, and the pH was adjusted at 4·5—5·0 when necessary by the addition of a few drops of concentrated ammonia. After 2 hr., the yeast was centrifuged in a Sharples Super-Centrifuge (25,000 r.p.m.), and the solid was suspended in peroxide-free ether (700 ml.) and vigorously stirred in a Waring blendor after the addition of ethanol (700 ml.). After centrifugation at moderate speed a clear, deep yellow, protein-free extract was obtained. Two phases were obtained on adding to this extract a further 500 ml. of ether, the alcohol phase being the more deeply coloured. The alcoholic solution was washed three times with ether; the ether and part of the ethanol were then removed *in vacuo*.

This alcoholic solution possessed an absorption maximum at 259 mμ, in agreement with the band attributed mainly to adenine by Ernster *et al.*,[1] but in contrast with their experience exhibited no absorption maximum at 325—330 mμ. Moreover, when a portion of this solution was taken to dryness under reduced pressure and extracted with chloroform, the extract gave no colour or cloudiness with the antimony trichloride reagent. Examination of the ether phase by similar methods revealed the presence of ergosterol but not of vitamin A.

The negative results of the above experiment made it necessary to examine yeast by the conventional and more sensitive method of direct saponification of the material followed by examination of the unsaponifiable fraction for vitamin A. Baker's yeast (500 g.) was incubated in an atmosphere of oxygen as previously described. After centrifugation, the yeast was heated on a water-bath with 60% (w/v) potassium hydroxide (0·5 ml./g. yeast) until the mixture became homogeneous. Ethanol (2 vol.) was then added and boiling was continued under reflux for 2 hr., whereupon water was added and the mixture was extracted (five times) with ether (freshly distilled over reduced iron). The combined ether extract was washed with water until free from alkali, dried (Na_2SO_4), filtered through a sintered glass funnel, and taken to dryness under nitrogen. The absorption spectrum of the residue showed the peaks at 263, 272, 282, and 293 mμ characteristic of the 7-dehydro-steroid chromophore, but in addition an inflexion at 327 mμ.

In order to investigate the origin of this inflexion, the unsaponifiable material was subjected to chromatographic fractionation on alumina (Grade O, P. Spence & Co., Ltd., Widnes) weakened with water to Brockmann Grade III. Ether, light petroleum ("AnalaR"; b. p. 40—60°), and mixtures of these two solvents were used as eluants. Both solvents were dried over

* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Ernster, Zetterström, and Lindberg, *Exp. Cell. Res.*, 1950, **1**, 494.

sodium wire and redistilled before use, the ether being redistilled over reduced iron. Fractions were taken to dryness under nitrogen and later examined spectroscopically in *cyclo*hexane. 4% and 6% Ether–light petroleum mixtures eluted yellow oily fractions characterised by absorption spectra with $\lambda_{max.}$ 272—273 mμ and a step-out at 330 mμ. These fractions gave no colour with the antimony trichloride reagent, and no evidence of the presence of vitamin A was obtained either spectroscopically or by the colour reaction in any of the other chromatographic fractions. Since these fractions exhibited no selective absorption in the visible region, the presence of carotenoids is excluded.

Untreated yeast (*i.e.*, yeast *not* subjected to incubation) was then examined by chromatography of the unsaponifiable matter as described above. Once again 4% ether–light petroleum mixture eluted a yellow oil with the same characteristic absorption but showing evidence of contaminants by ergosteryl esters. In order to eliminate impurities rechromatography on alumina was necessary. This gave material with $E^{1\%}_{1\ cm.}$ 167 at 272 mμ, which also exhibited an inflexion at 330 mμ and a very weak inflexion near 410 mμ. A close estimate of the concentration of this substance in the yeast could not be made because, in the effort to characterise it, yield was sacrificed to purity.

Festenstein, Heaton, Lowe, and Morton [1] have described the properties of a yellow substance which is also eluted from alumina (weakened with water to Brockmann Grade III) by 4—6% ether–light petroleum. This material was designated " SA " by Festenstein *et al.*,[1] who also detected it in pig intestine, horse stomach and intestine, and rat liver, kidney, small intestine, and submaxillary gland. The spectroscopic properties of rat-liver SA and the purest material

Substance "SA" from rat liver and from yeast.

		Rat liver	Yeast * *a*	Yeast * *b*
In *cyclo*hexane: $E^{1\%}_{1\ cm.}$ at $\lambda_{max.}$ (272 mμ)		174	167	126
$\lambda_{min.}$ (235 mμ)		37	68·2	31·2
$\lambda_{infl.}$ (330 mμ)		12·3	15·2	8·2
$\lambda_{v.w.\ infl.}$ (410 mμ)		7·5	7·1	4·8
			a	
$\lambda_{max.}$ in: light petroleum		272	271	
$CHCl_3$		277—278	277—278	
EtOH		275	275	
HCl–EtOH		275	274—275	
KOH–EtOH		Peak disappears		
	λ (mμ)	$E^{1\%}_{1\ cm.}$	λ (mμ)	$E^{1\%}_{1\ cm.}$
In conc. H_2SO_4 after 30 min. in darkness at room temp.: max.	313—315	337	311	335
infl.	335	182	355	162
	420	66·7	415—425 †	93·6
E_{315} (H_2SO_4)/E_{273} (*cyclo*hexane)	1·99		2·01	

* *a*, Most intensely absorbing prepn.; *b*, qualitatively best spectrum.
† Weak max., not shown in rat-liver prepn.

obtained from yeast are compared in the Table. The agreement is excellent except for solutions in concentrated sulphuric acid. The material from yeast exhibits a weak maximum near 420 mμ not observed with the rat-liver material. This may be due to an impurity in the yeast preparation, which had a slightly lower extinction ($E^{1\%}_{1\ cm.}$ 167 at 272 mμ) than the rat-liver material ($E^{1\%}_{1\ cm.}$ 174 at 272 mμ).

Biochemistry Department, University of Liverpool. [*Received, April 11th*, 1956.]

[1] Festenstein, Heaton, Lowe, and Morton, *Biochem. J.*, 1955, **59**, 558.

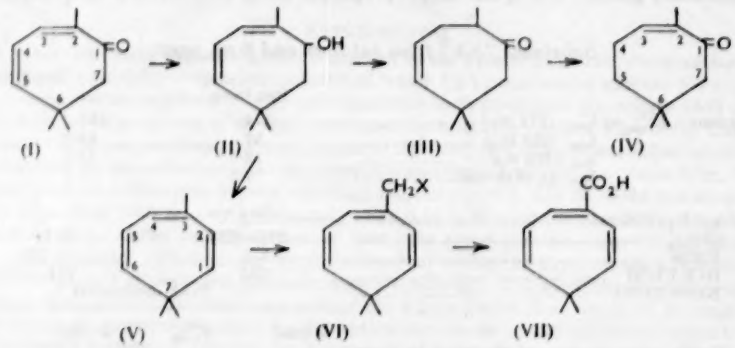
791. *Elaboration Products of Eucarvone.**

By J. R. B. Campbell, A. M. Islam, and R. A. Raphael.

Eucarvone has been converted into thujic acid. Selenium dioxide oxidises eucarvone and α-dihydroeucarvone in an unexpected fashion, producing hydroxy-ketones.

Although eucarvone (I) was one of the first *cyclo*heptane derivatives to be prepared [1] its reactions have not been explored during the recent intensive study of this ring system. This is all the more surprising as its carbon skeleton is identical with that of thujic acid (VII), the interesting *cyclo*heptatriene derivative which occurs together with the thujaplicins in the heart-wood of the Western red cedar (*Thuja plicata* D. Don).[2] Although thujic acid has been synthesised from 4 : 4-dimethyl*cyclo*heptanone [3] the bromination–dehydrobromination procedure employed was not unequivocal from the structural point of view and the yield was small. It was decided, therefore, to attempt a conversion of eucarvone into thujic acid.

Reduction of eucarvone with lithium aluminium hydride gave the expected 2 : 6 : 6-trimethyl*cyclo*hepta-2 : 4-dien-1-ol (II). However, if care was not taken during the



(I) (II) (III) (IV) (V) (VI) (VII)

working up, this product isomerised almost completely to α-dihydroeucarvone (III) which had previously been prepared by reduction of eucarvone with sodium and alcohol and oxidation of the monounsaturated alcohol thus produced.[4] [Although (III) was the structure proposed by the earlier workers, it is pertinent to note that the alternative position of the ·CH=CH· grouping is not excluded by the properties of the compound and has certain mechanistic advantages.[5]] This prototropic rearrangement took place in almost quantitative yield when the alcohol (II) was distilled with a trace of sulphuric acid. More drastic acid treatment of both the alcohol (II) and the ketone (III) led to a further rearrangement giving the conjugated ketone, β-dihydroeucarvone (IV). This sensitivity of alcohol (II) towards acidic reagents meant that the use of such reagents to achieve dehydration to the *cyclo*heptatriene (V) met with only limited success. Heating the alcohol with potassium hydrogen sulphate, dipotassium pyrosulphate, or toluene-*p*-sulphonic acid gave a small yield of the hydrocarbon (V) but the major product was α- or β-dihydroeucarvone, depending on the temperature used. Conversion of the alcohol (II) into the corresponding chloro-compound, followed by dehydrochlorination under various

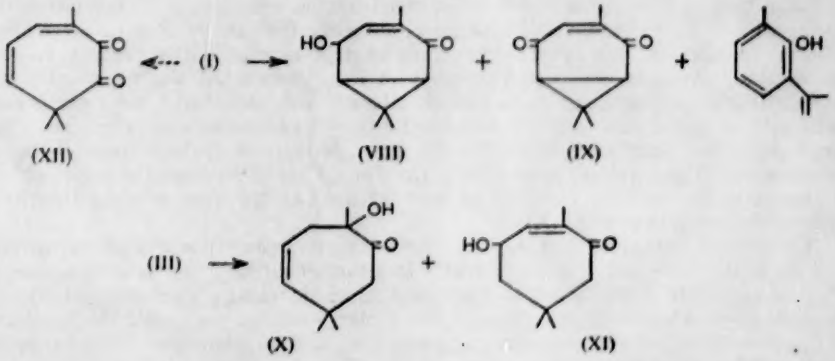
* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Baeyer, *Ber.*, 1894, **27**, 810; Wallach, *Annalen*, 1905, **339**, 94.
[2] Gripenberg, *Acta Chem. Scand.*, 1949, **3**, 1137.
[3] *Idem*, *ibid.*, 1951, **5**, 995; 1952, **6**, 854.
[4] For references see Simonsen, "The Terpenes," Vol. II, Cambridge Univ. Press, 1949, pp. 86—94.
[5] We thank Professor D. H. R. Barton, F.R.S., for discussions of this point.

conditions, failed to give this triene (V). Finally a good yield of triene (V) was obtained by the dehydration of the alcohol with boric acid.[6] The structure of the triene (V) was confirmed by its light-absorption properties, by its oxidation to dimethylmalonic acid, and by its hydrogenation to 1 : 1 : 4-trimethyl*cyclo*heptane, identified by comparison with an authentic sample. Treatment of the hydrocarbon (V) with *N*-bromosuccinimide gave the bromo-derivative (VI; X = Br) which was converted into the corresponding acetoxy-compound (VI; X = OAc) by tetraethylammonium acetate, a reagent which accomplishes replacement of an allylic bromine atom without the incursion of an anionotropic rearrangement.[7] Methanolysis of the acetate gave the corresponding alcohol (VI; R = OH) which was then oxidised with chromium trioxide in the cold. Steam-distillation of the crude product gave a small yield of thujic acid (VII), identical with the naturally occurring compound.

In view of the current interest in tropolones it was thought interesting to attempt the oxidation of eucarvone to the α-diketone (XII), in which the *gem.*-dimethyl group blocks enolisation to a true tropolone.

Treatment of eucarvone with the obvious reagent, selenium dioxide, gave as main product a conjugated hydroxy-ketone (VIII); by-products were a conjugated enedione



(IX), and a mixture of phenols of which 2-methyl-6-*iso*propenylphenol was identified as one component by isolation of its dimer. The key reaction in the determination of the structure of the hydroxy-ketone (VIII) was the production of *cis*-caronic acid on oxidation. A detailed description of the argument in favour of structure (VIII) is not given as this part of the work has been anticipated by a recent publication which gives other examples of reactions of eucarvone involving similar ring-bridging.[8]

As this direct route to the diketone (XII) had failed, an indirect approach was tried, namely, oxidation of α-dihydroeucarvone (III) by selenium dioxide to an α-diketone which should be convertible by dehydrogenation into (XII). It was felt that the "insulation" between the carbonyl group and the double bond in α-dihydroeucarvone would render rearrangements less likely. In practice this reaction gave two isomeric hydroxy-ketones, $C_{10}H_{16}O_2$, readily separable by a remarkably large difference in boiling point. Their structural assignment as (X) and (XI) was shown by the following evidence. The ultraviolet and infrared absorption of the compound (XI) indicated it to be a hydroxylated αβ-unsaturated ketone containing a trisubstituted double bond. Treatment with manganese dioxide converted it into an enedione, thus showing the hydroxyl group to be both secondary and allylic. It was unaffected by periodic acid, but ozonolysis and

[6] Brandenberg and Galat, *J. Amer. Chem. Soc.*, 1950, **72**, 3275.
[7] Owen and Smith, *J.*, 1952, 4035.
[8] Corey, Burke, and Remers, *J. Amer. Chem. Soc.*, 1956, **78**, 174, 180; cf. Campbell, Baldoni, and Campbell, Abs. 119th Meeting of the Amer. Chem. Soc., 1951, p. 6L.

oxidation of the ozonide produced ββ-dimethylglutaric acid. All these reactions are fully compatible with the formulation (XI) and this was confirmed by dehydration of the compound whereby eucarvone was produced in good yield.

The light-absorption properties of the isomer (X) indicated it to be a hydroxylated, non-conjugated ketone containing a disubstituted *cis*-double bond. It was unaffected by manganese dioxide but was quantitatively cleaved by 1 mol. of periodic acid, thus indicating that the hydroxyl and the carbonyl group were vicinal. As the compound was not affected by bismuth oxide,[9] a specific reagent for the oxidation of secondary α-hydroxy-ketones, the presence of a tertiary α-hydroxy-ketone system was suggested. Permanganate oxidation of the compound (X) gave αα-dimethylsuccinic acid. These findings point to the structure (X) for this product (as in the starting α-dihydroeucarvone, a $\Delta^{3:4}$-structure is an alternative possibility). Inspection of this structure suggested that it too should yield eucarvone on dehydration. Although the product of this reaction was isomeric with eucarvone and closely resembled the latter in physical properties, the derivatives of the two ketones were not identical. Further, the tetrahydro-derivative of the new ketone was not tetrahydroeucarvone (2 : 6 : 6-trimethyl*cyclo*heptanone), thus indicating that a skeletal rearrangement had taken place. (An attractive hypothesis to account for these facts is the occurrence of a transannular Nametkin rearrangement to give 3 : 7 : 7-trimethyl*cyclo*hepta-2 : 4-dien-1-one. This possibility was disproved by the non-identity of the tetrahydroketone with 2 : 2 : 6-trimethyl*cyclo*heptanone, authentic derivatives of which were kindly supplied by Dr. O. Jeger.) The structure of this rearrangement product is being investigated. Another unexpected property of this product (X) was its reaction with 2 : 4-dinitrophenylhydrazine; in methanol, ethanol, and acetic acid the corresponding methoxy-, ethoxy-, and acetoxy-2 : 4-dinitrophenylhydrazones were obtained. More surprisingly the ultraviolet absorption of these derivatives showed them to be αβ-unsaturated. The simplest explanation is that, in the acidic medium, the compound (X) undergoes an anionotropic replacement rearrangement to the corresponding substituted hydroxy-ketone derived from (XI).

The above results show that the 7-methylene group in eucarvone and its derivatives is well shielded by the *gem.*-dimethyl group. In a further attempt to attack this protected site, use was made of the finding that *N*-iodosuccinimide reacts with enol acetates to give α-iodo-ketones, whereas other carbon–carbon double bonds are unaffected.[10] Application of this reaction to the enol acetate of eucarvone (prepared by interaction of the ketone and *iso*propenyl acetate) gave no pure compound.

Experimental

Ultraviolet spectra were determined with a Unicam SP500 Spectrophotometer, and infrared spectra with a Perkin–Elmer Model 21 Spectrophotometer. Only the important maxima in the infrared spectra are recorded.

Eucarvone (I).—This was prepared in 65% yield from carvone by Wallach's method.[1] It had b. p. 82—84°/8 mm., n_D^{25} 1·5065, $\lambda_{max.}$ (in MeOH) 300 mμ (log ε 3·82), $\nu_{max.}$ (thin film) 1660 (conjugated C=O), 1387, 1364 (CMe_2), 828 cm.$^{-1}$ (>C=CH–). The 2 : 4-dinitrophenylhydrazone, red plates (from ethanol–ethyl acetate), had m. p. 151—152°, $\lambda_{max.}$ (in $CHCl_3$) 388 mμ (log ε 4·44).

2 : 6 : 6-*Trimethyl*cyclo*hepta*-2 : 4-*dien*-1-*ol* (II).—To a stirred slurry of powdered lithium aluminium hydride (6 g.) in ether (200 ml.) was added, during 30 min., a solution of eucarvone (20 g.) in ether (100 ml.). After a further 10 min. the excess of hydride was destroyed by addition of ethyl acetate, followed by water. The solids were dissolved by adding the minimum amount of ice-cold 5% sulphuric acid. Ether-extraction, washing (sodium hydrogen carbonate solution and water), drying ($MgSO_4$), and distillation gave the *alcohol* (18·5 g., 92%), b. p. 94—97°/10 mm., n_D^{18} 1·4980, $\lambda_{max.}$ (in MeOH) 248·5 mμ (log ε 3·76), (in hexane) 248 mμ (log ε 3·56) [cf. *cyclo*hepta-1 : 3-diene : [11] $\lambda_{max.}$ (in *iso*octane) 248 mμ (log ε 3·87)], $\nu_{max.}$ (thin film) 3375 (OH), 1647 (–CH=CH–), 1380, 1368 (CMe_2), 1032 cm.$^{-1}$ (C–OH) (Found: C, 78·55; H, 10·3. $C_{10}H_{16}O$

[9] Rigby, *J.*, 1951, 793.
[10] Djerassi and Lenk, *J. Amer. Chem. Soc.*, 1953, **75**, 3493.
[11] Pesch and Friess, *ibid.*, 1950, **72**, 5756.

requires C, 78·9; H, 10·6%). The *phenylurethane*, m. p. 110—111°, crystallised from light petroleum (b. p. 60—80°) in needles (Found: N, 5·4. $C_{17}H_{21}O_2N$ requires N, 5·15%).

It is essential in the working-up that the time of contact with acid be kept to a minimum and that the temperature be kept below 5° in order to avoid extensive isomerisation of the product to α-dihydroeucarvone (see below).

Interconversions of the Alcohol (II), *α-Dihydroeucarvone* (III), *and β-Dihydroeucarvone* (IV).—(*a*) The alcohol (II) (2 g.) was distilled in the presence of a trace of sulphuric acid (one drop of a 10% ethanolic solution). Fractionation of the distillate gave α-dihydroeucarvone (III) (1·72 g., 86%), b. p. 74—76°/9 mm., n_D^{17} 1·4686, $\lambda_{max.}$ (in MeOH) 290 mμ (log ε 1·57), $\nu_{max.}$ (thin film) 1708 (non-conjugated C=O), 1370, 1390 (CMe_2), 689 cm.$^{-1}$ (*cis* –CH=CH–). The semicarbazone formed needles, m. p. 188—189°, from aqueous ethanol (lit.,[4] m. p. 189—191°). The 2 : 4-*dinitrophenylhydrazone*, prepared by using a solution of 2 : 4-dinitrophenylhydrazine in acetic acid, crystallised from ethanol in yellow prisms, m. p. 120—121°, $\lambda_{max.}$ (in $CHCl_3$) 367 mμ (log ε 4·38) (Found: C, 58·0; H, 6·25; N, 16·9. $C_{16}H_{20}O_4N_4$ requires C, 57·8; H, 6·05; N, 16·85%). If the reagent was used in the more usual medium of ethanolic sulphuric acid the 2 : 4-dinitrophenylhydrazone of β-dihydroeucarvone (see below) was obtained.

(*b*) The alcohol (II) (5 g.) was distilled in the presence of toluene-*p*-sulphonic acid; a considerable quantity of resin remained in the flask. Fractionation of the distillate gave β-dihydroeucarvone (IV) (3·5 g., 70%), b. p. 78—79°/7 mm., n_D^{25} 1·4777, $\lambda_{max.}$ (in MeOH) 239 mμ (log ε 3·79), $\nu_{max.}$ (thin film) 1664 (conjugated C=O), 835 cm.$^{-1}$ (>C=CH–). The semicarbazone formed needles, m. p. 203—204° (decomp.; sealed tube), from aqueous ethanol (lit.,[4] m. p. 202°), and the oxime plates, m. p. 121—122°, from aqueous ethanol (lit.,[4] m. p. 122°). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange-red plates, m. p. 194—195°, $\lambda_{max.}$ (in $CHCl_3$) 380·5 mμ (log ε 4·4) (Found: C, 57·7; H, 5·85; N, 16·9%).

(*c*) α-Dihydroeucarvone (10 g.), ethanol (25 ml.), and concentrated sulphuric acid (1 ml.) were heated under reflux for 45 min. The mixture was poured into saturated sodium carbonate solution, and the product isolated by means of ether. Drying ($MgSO_4$) and distillation gave β-dihydroeucarvone (IV) (9·2 g., 92%), b. p. 86—88°/11 mm., n_D^{25} 1·4773, identified further by its derivatives described under (*b*).

7-Chloro-1 : 5 : 5-trimethylcyclohepta-1 : 3-diene.—To an ice-cold solution of alcohol (II) (5 g.) and dimethylaniline (6 g.) in chloroform (10 ml.), was added during 30 min. with stirring a solution of thionyl chloride (5 g.) in chloroform. After 10 hr. at −10° the mixture was shaken with ice-cold N-hydrochloric acid (50 ml.) and extracted with chloroform. Washing (sodium hydrogen carbonate solution and water), drying ($MgSO_4$), and distillation gave the fragrant *chloro-compound* (3·9 g., 70%), b. p. 78—80°/8 mm., n_D^{18} 1·4992, $\lambda_{max.}$ (in MeOH) 243 mμ (log ε 3·48) (Found: C, 70·05; H, 8·85; Cl, 20·4. $C_{10}H_{15}Cl$ requires C, 70·35; H, 8·85; Cl, 20·8%). The compound gradually polymerised to a dark resin.

3 : 7 : 7-*Trimethylcyclohepta-1 : 3 : 5-triene* (V).—A mixture of the alcohol (II) (20 g.) and boric acid (10 g.) was gradually heated until it became homogeneous; the bath-temperature was then raised rapidly to 350°. The distillate was dissolved in light petroleum (b. p. 40—60°) and dried ($MgSO_4$), and the solvent removed through a column. Fractionation gave the *hydrocarbon* (V) (11 g., 61%) as a mobile liquid, b. p. 62°/20 mm., n_D^{20} 1·4948, $\lambda_{max.}$ (in hexane) 268 mμ (log ε 3·4) (cf. *cyclo*hepta-1 : 3 : 5-triene :[13] $\lambda_{max.}$ 260 mμ), $\nu_{max.}$ (thin film) 1625, 1610 (C=C), 1375, 1360 (CMe_2), 816 (>C=CH–), 664 cm.$^{-1}$ (*cis* –CH=CH–). The hydrocarbon gave a deep red colour with tetranitromethane in carbon tetrachloride (Found: C, 89·6; H, 10·7. $C_{10}H_{14}$ requires C, 89·5; H, 10·5%). A higher-boiling fraction from the preparation (4·6 g.), b. p. 82°/12 mm., n_D^{19} 1·4699, proved to be α-dihydroeucarvone, identified by its derivatives described above.

The hydrocarbon (V) (1 g.) and maleic anhydride (0·8 g.) were heated together in a sealed tube for 3 hr. at 100°. The resulting pasty mass was treated with the solvent system light petroleum–benzene–methanol–water in the manner described by Lythgoe *et al.*[13] Drying and evaporation of the combined top layers gave a gum which solidified on being triturated with ethanol. Crystallisation from the same solvent gave the *adduct* as prisms, m. p. 112—114° (Found: C, 71·95; H, 6·4. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·95%); microhydrogenation showed 2·08 double bonds. Oxidation of the hydrocarbon (V) (1 g.) in benzene solution with aqueous potassium permanganate buffered with carbon dioxide gave dimethylmalonic acid (60 mg.), m. p. and mixed m. p. 189—191° (decomp.; rapid heating); decarboxylation gave *iso*butyric acid, identified as its *S*-benzylthiuronium salt, m. p. and mixed m. p. 141—143°.

[13] Dryden, *J. Amer. Chem. Soc.*, 1954, **76**, 2841.
[13] Anet, Lythgoe, Silk, and Trippett, *J.*, 1953, 320.

1 : 1 : 4-*Trimethylcycloheptane*.—(*a*) Catalytic hydrogenation of eucarvone in ethanol over 10% palladium–charcoal gave a quantitative yield of 2 : 6 : 6-trimethyl*cyclo*heptanone,[4] b. p. 79—80°/12 mm., n_D^{19} 1·4558, $\nu_{max.}$ (thin film) 1700 (C=O), 1383, 1369 cm.$^{-1}$ (CMe_2); the 2 : 4-*dinitrophenylhydrazone*, purified by chromatography in light petroleum on kieselguhr–bentonite,[14] crystallised from light petroleum (b. p. 60—80°) in orange plates, m. p. 137—137·5°, $\lambda_{max.}$ (in $CHCl_3$) 365 mμ (log ε 4·34) (Found: C, 57·7; H, 6·35; N, 16·45. $C_{18}H_{22}O_4N_4$ requires C, 57·45; H, 6·65; N, 16·75%). The saturated ketone (3·5 g.), 60% hydrazine hydrate (5 ml.), sodium hydroxide (2·3 g.), and diethylene glycol (20 ml.) were heated under reflux for 2 hr. (internal temp. 137°). The mixture was then distilled until the internal temperature reached 200° and the distillate was set aside. The residual solution was then heated under reflux for 12 hr., combined with the distillate, diluted with water (100 ml.), and extracted with ether. The combined extracts were washed with 2N-hydrochloric acid and water and dried ($MgSO_4$). Evaporation and distillation gave 1 : 1 : 4-*trimethylcycloheptane* (1·8 g., 59%), b. p. 72—72·5°/35 mm., n_D^{15} 1·4438 (Found: C, 85·45; H, 14·4. $C_{10}H_{20}$ requires C, 85·65; H, 14·35%), $\nu_{max.}$ 2920 (CH stretching), 1462 (CH deformation), 1383, 1364 (CMe_2 deformation), 1182, 814 cm.$^{-1}$ (CMe_2 skeletal).

(*b*) A solution of the trimethyl*cyclo*heptatriene (V) (1·32 g.) in acetic acid (10 ml.) was hydrogenated over platinic oxide (200 mg.); after 3 mols. of hydrogen had been absorbed reaction ceased. The filtered solution was poured into excess of saturated sodium carbonate solution. The organic layer was dried and distilled, to give a product (1·1 g.), b. p. 86°/56 mm., n_D^{25} 1·4412. The infrared spectrum was identical with that of 1 : 1 : 4-trimethyl*cyclo*heptane prepared as in (*a*).

Thujic Acid (VII).—A mixture of the trimethyl*cyclo*heptatriene (1 g.), carbon tetrachloride (10 ml.), chloroform (3 ml.), powdered *N*-bromosuccinimide (1·3 g.), and a trace of benzoyl peroxide was heated under reflux for 20 min., by which time all the solids were floating on the surface of the liquid. The mixture was cooled to 0°, the succinimide (0·7 g., 97%) was filtered off, and the filtrate freed from solvents under reduced pressure. The crude 3-bromomethyl-7 : 7-dimethyl*cyclo*hepta-1 : 3 : 5-triene (VI; X = Br) (1·5 g.) in acetone (10 ml.) was added slowly to a solution of tetraethylammonium acetate (5 g.) in acetone (50 ml.) with cooling to <5°. The orange solution deposited tetraethylammonium bromide overnight. The bromide was filtered off and washed with acetone; the combined filtrates were concentrated under reduced pressure. Addition of water and isolation by means of ether gave 3-acetoxymethyl-7 : 7-dimethyl*cyclo*hepta-1 : 3 : 5-triene (VI; X = OAc) (1·0 g.), b. p. 94—97°/12 mm., n_D^{19} 1·5435. This product was added to methanolic sodium methoxide [from sodium (0·1 g.) and methanol (20 ml.)] and set aside at room temperature for 18 hr. Dilution with water and isolation by means of ether gave 3-hydroxymethyl-7 : 7-dimethyl*cyclo*hepta-1 : 3 : 5-triene (0·35 g.), b. p. 100—102°/12 mm., $n_D^{19\cdot5}$ 1·5200. A solution of this hydroxy-compound in acetone (10 ml.) was treated with a solution of chromium trioxide (0·31 g.) in water (20 ml.), the temperature being kept below 20°. After 1 hr. the mixture was thoroughly extracted with ether and the extracts were shaken with sodium carbonate solution; acidification by dilute sulphuric acid and isolation with ether gave an acidic gum (80 mg.) which crystallised. This product was steam-distilled in nitrogen; the distillate was cooled to 0° and the resulting solid (40 mg.) filtered off and dried. Repeated crystallisation from light petroleum (b. p. 40—60°) gave thujic acid as needles, m. p. 78—80° undepressed on admixture with an authentic sample of the naturally occurring material (m. p. 81—82°). The infrared absorptions of the natural and the synthetic material were almost identical: $\nu_{max.}$ (in CS_2) 2980, 1690, 1415, 1380, 1365, 1285, 1260, 1200, 1095, 1040, 935, 825, 760, 740, 725, 670 cm.$^{-1}$. Isomerisation by heating the synthetic product with concentrated hydrochloric acid for 30 min. gave cumic acid, m. p. 114—116° undepressed on admixture with an authentic specimen (m. p. 114—116°). (The intermediates in the above preparation rapidly polymerised.)

Oxidation of Eucarvone by Selenium Dioxide.—A solution of eucarvone (30 g.) and selenium dioxide (22·2 g.) in ethanol (550 ml.) and water (20 ml.) was heated under reflux for 16 hr. The solution was concentrated to 100 ml., the precipitated selenium filtered off, and the filtrate poured into N-sulphuric acid (1 l.). Extraction with chloroform gave an oil which was heated in benzene (250 ml.) under reflux with silver powder (30 g.); filtration and evaporation gave a viscous, red oil which partially solidified. As direct crystallisation was attended by considerable loss the crude product was freed from high-boiling selenium-containing by-products by flash-distillation under a high vacuum. The distillate (21·3 g.), b. p. 40—180°/0·1 mm., was treated

[14] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.

with light petroleum (40 ml.; b. p. 40—60°) and set aside at −10°. The crystals thus obtained were crystallised from light petroleum (b. p. 60—80°), to give 3 : 7 : 7-*trimethyl*bicyclo[4 : 1 : 0]-*hept*-3-*en*-5-*ol*-2-*one* (VIII) (4·7 g.) as prisms, m. p. 85—86°, $\lambda_{max.}$ (in MeOH) 229 mμ (log ε 4·04) (Found: C, 72·3%; H, 8·4. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%).

The petroleum mother-liquors were extracted with 10N-sodium hydroxide, and the extracts acidified with hydrochloric acid. Isolation by means of ether gave a phenolic fraction (5·9 g.), b. p. 86—87°/10 mm., n_D^{25} 1·5392. A portion of this product was heated with iodine at 60° for 30 min. and steam-distilled. Crystallisation of the solid steam-distillate from light petroleum (b. p. 60—80°) gave prisms, m. p. 68—70°, undepressed by an authentic sample of 2′-hydroxy-2 : 4 : 4 : 8 : 3′-pentamethylflavan (m. p. 69—70°); the acetyl derivatives (m. p. 101—102°) were also identical.[15]

Evaporation and distillation of the petroleum mother-liquors after alkaline extraction gave unchanged eucarvone (1·9 g.), b. p. 80—82°/8 mm., and a higher-boiling fraction, b. p. 115—120°/9 mm. which partially solidified. Crystallisation from light petroleum (b. p. 80—100°) gave massive yellow prisms (1·2 g.), m. p. 91—92°, of 3 : 7 : 7-*trimethyl*bicyclo[4 : 1 : 0]*hept*-3-*ene*-2 : 5-*dione* (IX) [identical with the product obtained by manganese dioxide oxidation of the hydroxy-ketone (VIII)], $\lambda_{max.}$ (in MeOH) 240 mμ (log ε 4·12) (Found: C, 73·6; H, 7·35. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·35%). The *mono*-2 : 4-*dinitrophenylhydrazone* crystallised from ethanol–benzene in orange-red plates, m. p. 171—173° (Found: N, 16·2. $C_{16}H_{16}O_5N_4$ requires N, 16·25%); the *bis*-2 : 4-*dinitrophenylhydrazone* formed scarlet needles, charring at *ca.* 250° (from nitrobenzene), $\lambda_{max.}$ (in $CHCl_3$) 408 mμ (log ε 4·7) (Found: C, 50·2; H, 3·95; N, 21·25. $C_{22}H_{20}O_8N_8$ requires C, 50·4; H, 3·85; N, 21·35%).

Oxidation of α-Dihydroeucarvone by Selenium Dioxide.—A solution of α-dihydroeucarvone (20 g.) and selenium dioxide (15·2 g.) in ethanol (300 ml.) and water (10 ml.) was heated under reflux for 16 hr. and the crude product isolated and freed from selenium as described in the above cognate preparation. Fractional distillation gave two products. The lower-boiling material (9·5 g.) was in the sequel shown to be 2-*hydroxy*-2 : 6 : 6-*trimethyl*cyclo*hept*-4-*en*-1-*one* (X), b. p. 88—90°/8 mm., n_D^{18} 1·4845, showing no intense absorption above 200 mμ, $\nu_{max.}$ (thin film) 3460 (OH), 1708 (non-conjugated C=O), 1660 (C=C), 1386, 1370 (CMe_2), 1070 (C–OH), 682 cm.$^{-1}$ (*cis* –CH=CH–) (Found: C, 71·95; H, 9·25. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). Microhydrogenation showed 1·1 double bonds. The *phenylurethane* crystallised from light petroleum (b. p. 80—100°) in stout needles, m. p. 131° (Found: C, 70·9; H, 7·45. $C_{17}H_{21}O_3N$ requires C, 71·05; H, 7·35%). With 2 : 4-dinitrophenylhydrazine the derivatives obtained differed in composition according to the solvent used; methanolic sulphuric acid gave an O-*methyl dinitrophenylhydrazone*, red tablets, m. p. 157—158° (from ethanol–ethyl acetate) (Found: C, 56·2; H, 6·3; N, 15·6. $C_{17}H_{22}O_5N_4$ requires C, 56·35; H, 6·1; N, 15·45%); ethanolic sulphuric acid gave the O-*ethyl analogue*, orange plates m. p. 150° (from ethanol–ethyl acetate), $\lambda_{max.}$ (in $CHCl_3$) 375 mμ (log ε 4·43) (Found: C, 57·55; H, 6·35; N, 14·7. $C_{18}H_{24}O_5N_4$ requires C, 57·45; H, 6·45; N, 14·9%); acetic acid gave the O-*acetyl analogue*, yellow or red plates (polymorphs), m. p. 179—180° (from ethanol–ethyl acetate), $\lambda_{max.}$ (in $CHCl_3$) 371 mμ (log ε 4·45) (Found: C, 55·1; H, 5·85; N, 14·6. $C_{18}H_{22}O_6N_4$ requires C, 55·4; H, 5·7; N, 14·35%).

The higher-boiling fraction (6 g.) proved to be 4-*hydroxy*-2 : 6 : 6-*trimethyl*cyclo*hept*-2-*en*-1-*one* (XI), b. p. 78—81°/0·1 mm., n_D^{18} 1·5004, λ_{max} (in MeOH) 237 mμ (log ε 3·81), $\nu_{max.}$ (thin film) 3420 (OH), 1666 (conjugated C=O), 1368 (CMe_2), 1042 (C–OH), 837 cm.$^{-1}$ (>C=CH–) (Found: C, 71·45; H, 9·25%). Microhydrogenation showed 0·96 double bond. The *phenylurethane* crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 141—141·5° (Found: C, 70·8; H, 7·55%); the 2 : 4-*dinitrophenylhydrazone* formed crimson prisms, m. p. 152° (from ethanol–ethyl acetate), $\lambda_{max.}$ (in $CHCl_3$) 373·5 mμ (log ε 4·41) (Found: C, 55·15; H, 5·75; N, 15·9. $C_{16}H_{20}O_6N_4$ requires C, 55·15; H, 5·75; N, 16·1%).

Oxidations of the Hydroxy-ketones (X) *and* (XI).—(a) *Periodic acid.* Separate samples (90 mg.) of the isomers were treated with aqueous 0·2M-periodic acid together with sufficient methanol to give homogeneity (a blank was performed simultaneously). After 30 hr. at 20° the solutions were treated with saturated sodium hydrogen carbonate solution (2 ml.), 0·2M-sodium arsenite (10 ml.), and 10% potassium iodide solution. After 15 min. the mixture was titrated with iodine solution. The results showed that compound (X) had consumed 0·91 mol. of periodic acid, whereas the isomer (XI) had only used 0·11 mol. A control with benzoin showed a consumption of 0·94 mol.

(b) *Chromium trioxide in acetic acid.* A solution of the compound (XI) (0·5 g.) and chromium

[15] Baker, Curtis, and McOmie, *J.*, 1952, 1774.

trioxide (0·2 g.) in acetic acid (5 ml.) and water (5 ml.) was kept at room temperature for 12 hr. Excess of oxidising agent was destroyed by methanol, and the product isolated with benzene. Distillation gave **2 : 6 : 6-*trimethylcyclohept-2-ene*-1 : 4-*dione*** (0·41 g.), b. p. 110—112°/9 mm., $n_D^{18\cdot5}$ 1·4948, $\lambda_{max.}$ (in MeOH) 244 mμ (log ε 3·95), $\nu_{max.}$ (thin film) 1672 (conjugated C=O), 1620 (C=C), 1372 (CMe_2), 834 cm.$^{-1}$ (>C=CH−) (Found : C, 71·8; H, 8·7. $C_{10}H_{14}O_2$ requires C, 72·2; H, 8·5%). The ***mono*-2 : 4-*dinitrophenylhydrazone*** formed orange needles, m. p. 190—191° (from ethanol–ethyl acetate), $\lambda_{max.}$ (in $CHCl_3$) 374·5 mμ (log ε 4·46) (Found : C, 55·6; H, 5·2; N, 16·0. $C_{16}H_{18}O_5N_4$ requires C, 55·5; H, 5·25; N, 16·2%); the ***bis*-2 : 4-*dinitrophenylhydrazone*** crystallised from acetic acid in red needles, m. p. 289° (decomp.), $\lambda_{max.}$ (in $CHCl_3$) 397 mμ (log ε 4·71) (Found : C, 49·8; H, 4·3; N, 21·0. $C_{32}H_{22}O_8N_8$ requires C, 50·2; H, 4·2; N, 21·3%).

Oxidation of the isomer (X) by the same procedure, followed by titration with ferrous ammonium sulphate solution, indicated the oxidising agent consumed to be 96% of that required for the fission of a tertiary α-hydroxy-ketone. No pure entity could be obtained from the products.

(c) ***Manganese dioxide.*** A solution of the compound (XI) (0·2 g.) in light petroleum (b. p. 40—60°) (25 ml.) was shaken with activated manganese dioxide [16] (2 g.) for 4 days. Filtration, evaporation, and distillation gave the diketone described under (b). The isomeric compound (X) was unaffected by this treatment.

(d) ***Potassium permanganate.*** Carbon dioxide was passed into a stirred suspension of the compound (X) (0·5 g.) in water (5 ml.) while a solution of potassium permanganate (2·5 g.) in water (40 ml.) was added during 1 hr., and the resulting mixture set aside overnight. Acidification and passage of sulphur dioxide, followed by isolation by means of ethyl acetate, gave a solid product which was recrystallised from benzene. It formed prisms (60 mg.), m. p. 139—141° undepressed on admixture with authentic αα-dimethylsuccinic acid. The same product was obtained by a similar oxidation of the isomer (XI).

(e) ***Ozone.*** Ozonised oxygen (0·6% of O_3) was passed for 4 hr. through a cooled (−30°) solution of compound (XI) (0·19 g.) in ethyl acetate (5 ml.). Any volatile products were collected in a water-trap; its contents gave no iodoform reaction or positive tests for formaldehyde. The solution was then hydrogenated over 10% palladium–charcoal (0·5 g.), the uptake of hydrogen being almost that required by theory. Removal of solvent under reduced pressure gave a solid residue which showed a strong iodoform reaction. This product was heated for 2 hr. with chromium trioxide (0·35 g.) in 50% acetic acid (10 ml.). Isolation by means of benzene and crystallisation from benzene–light petroleum (b. p. 60—80°) gave ββ-dimethylglutaric acid as prismatic needles, m. p. and mixed m. p. 101°.

***Dehydration of the Isomers* (X) *and* (XI).**—(*a*) A mixture of compound (XI) (0·5 g.) and boric acid (0·2 g.) was heated by a free flame until no further distillate could be obtained. Working up as in the above cognate dehydration and distillation gave a product, b. p. 81—82°/8 mm., n_D^{17} 1·5160, which was shown by its light absorption and properties of its derivatives to be eucarvone.

(*b*) A mixture of the isomer (X) (1·5 g.) and boric acid (0·55 g.) was heated and the product worked up as under (*a*). Distillation gave a pale yellow oil (1·02 g., 74%), b. p. 88—89°/11 mm., n_D^{15} 1·5040, λ_{max} (in MeOH) 299 mμ (log ε 3·7), $\nu_{max.}$ (thin film) 1668 (conjugated C=O), 1384, 1360 (CMe_2), 828 (>C=CH−), 676 cm.$^{-1}$ (*cis* −CH=CH−) (Found : C, 79·8; H, 9·5. $C_{10}H_{14}O$ requires C, 79·95; H, 9·4%). The product gave negative iodoform and Schiff's tests. The **2 : 4-*dinitrophenylhydrazone*** crystallised from ethanol–ethyl acetate in crimson needles, m. p. 172—173° (depressed 40° by admixture with eucarvone 2 : 4-dinitrophenylhydrazone), $\lambda_{max.}$ (in $CHCl_3$) 396 mμ (log ε 4·45) (Found : C, 58·1; H, 5·9; N, 16·8. $C_{16}H_{18}O_4N_4$ requires C, 58·15; H, 5·5; N, 16·95%). Oxidation of the ketone with chromium trioxide or ozone by the procedures already described gave αα-dimethylsuccinic acid; no formaldehyde was detected. Catalytic hydrogenation of the ketone with 10% palladium–charcoal ceased after 2·0 mols. of hydrogen had been absorbed. The saturated ketone had b. p. 90°/15 mm., n_D^{25} 1·4520, $\nu_{max.}$ (thin film) 1707 (C=O), 1386, 1367 cm.$^{-1}$ (CMe_2). The **2 : 4-*dinitrophenylhydrazone*** crystallised from light petroleum (b. p. 80—100°) in orange plates, m. p. 115—118°, $\lambda_{max.}$ (in $CHCl_3$) 364 mμ (log ε 4·34) (Found : C, 57·7; H, 6·2. $C_{16}H_{22}O_4N_4$ requires C, 57·45; H, 6·65%).

Enol Acetate of Eucarvone.—A mixture of eucarvone (25 g.), *iso*propenyl acetate (150 ml.), and toluene-*p*-sulphonic acid (2 g.) was heated under a 12″ Vigreux column at such a rate that slow distillation took place; fresh *iso*propenyl acetate (100 ml.) was added slowly to maintain the total volume above 100 ml. After 15 hr. solid sodium hydrogen carbonate (20 g.) was added and the excess of reagent evaporated off under reduced pressure. The residual dark oil was

[16] Weedon, *Ann. Reports*, 1952, **49**, 142.

taken up in ether, filtered, washed with sodium hydrogen carbonate solution, and dried. Distillation gave the *enol acetate* (28·7 g., 90%), b. p. 110°/10 mm., n_D^{25} 1·4926, $\lambda_{max.}$ (in hexane) 268 mμ (log ε 3·43) (Found : C, 74·95; H, 8·05. $C_{12}H_{16}O_3$ requires C, 74·95; H, 8·4%).

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THE QUEEN'S UNIVERSITY, BELFAST. [*Received, April 12th,* 1956.]

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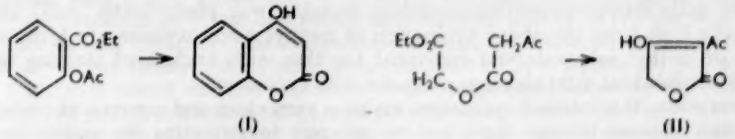
792. *Tetronic Acids and Related Compounds. Part I. Synthesis from α-Hydroxy-esters.**

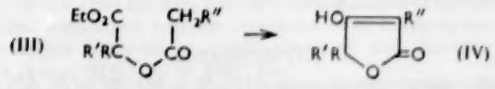
By L. J. HAYNES and A. H. STANNERS.

Cyclisation of α-acetoxy- and α-phenylacetoxy-esters by an internal Claisen ester reaction is investigated as a route to the synthesis of tetronic acids. The reaction proceeds very satisfactorily with esters of hydroxy-esters in which the hydroxyl group is tertiary when di*iso*propylamino-magnesium bromide is used as the condensing agent.

SEVERAL methods for the preparation of tetronic acids have been described : all depend on preparation of a γ-hydroxy-, γ-acetoxy-, or γ-halogeno-β-keto-ester and subsequent closure of the lactone ring. One standard route for the preparation of 4-hydroxycoumarin (I), which is formally related to a tetronic acid, is cyclisation of ethyl *o*-acetoxybenzoate by treatment with sodium,[1] an internal Claisen ester condensation taking place. Surprisingly, however, this type of reaction in which the O·CO of the lactone ring is not involved in the cyclisation, has received no attention as a route to tetronic acids save for a recent paper by Lacey [2] which described the cyclisation of acetoacetic esters derived by the action of diketen on α-hydroxy-esters to give acetyltetronic acids, *e.g.*, (II). An interest in tetronic acids led us to examine the internal Claisen condensation of the simple esters of α-hydroxy-esters.



(I) (II)



(III) (IV)

In our first attempt, ethyl acetoxyacetate (III; R = R′ = R″ = H) was treated with metallic sodium without solvent : there was little if any reaction at room temperature, but vigorous reaction at about 120°. The sodium dissolved completely, a brown solid (presumably a sodio-derivative) separated, and ethyl acetate appeared to be formed. However, cautious treatment of the solid with mineral acid gave no material giving a positive ferric chloride reaction and no tetronic acid could be isolated. Similar results were obtained with ethyl α-acetoxypropionate. We therefore turned to phenylacetates

* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] (*a*) Pauly and Lockemann, *Ber.*, 1915, **48**, 28; (*b*) Stahmann, Wolff, and Link, *J. Amer. Chem. Soc.*, 1943, **65**, 2285.

[2] Lacey, *J.*, 1954, 832.

of α-hydroxy-esters in the hope that the activation of the methylene group by the adjacent phenyl group would facilitate the cyclisation.

Treatment of ethyl (phenylacetoxy)acetate (III; R = R′ = H, R″ = Ph) in xylene with sodium at 140° resulted in a *ca.* 20% yield of α-phenyltetronic acid (IV; R = R′ = H, R″ = Ph). Similarly ethyl α-(phenylacetoxy)propionate (III; R = Me, R′ = H, R″ = Ph) gave γ-methyl-α-phenyltetronic acid (IV; R = Me, R′ = H, R″ = Ph) in 24% yield, and ethyl α-phenyl-α-(phenylacetoxy)acetate (III; R = H, R′ = R″ = Ph) gave αγ-diphenyltetronic acid (IV; R = H, R′ = R″ = Ph) in 34% yield. Ethyl phenylacetoxysuccinate (III; R = CH_2·CO_2Et, R′ = H, R″ = Ph) under these conditions gave no identifiable products apart from phenylacetic acid. The ester (III; R = Me, R′ = H, R″ = CO_2Et) from ethoxycarbonylacetyl chloride and ethyl lactate gave a small quantity of γ-methyltetronic acid: presumably the initial product, α-ethoxycarbonyl-γ-methyltetronic acid (IV; R = Me, R′ = H, R″ = CO_2Et), underwent hydrolysis and decarboxylation during the isolation or during the reaction.

We then turned our attention to the reagent used to effect the cyclisation. The use of di*iso*propylaminomagnesium bromide to effect Claisen ester condensations was first described by Frostick and Hauser,[3] and recently Royals and Turpin [4] have found that this reagent is very effective in promoting mixed ester condensations. It also proved more suitable than sodium for our purpose. Ethyl α-(phenylacetoxy)propionate gave a 60% yield of γ-methyl-α-phenyltetronic acid, and ethyl α-(phenylacetoxy)phenylacetate gave a 58% yield of αγ-diphenyltetronic acid, although ethyl (phenylacetoxy)acetate gave only a 21% yield of α-phenyltetronic acid. Still better yields were obtained in the cyclisations of phenylacetates of hydroxy-esters in which the hydroxyl group was tertiary: thus ethyl α-methyl-α-(phenylacetoxy)propionate (III; R = R′ = Me, R″ = Ph) gave a 65% yield of γγ-dimethyl-α-phenyltetronic acid (IV; R = R′ = Me, R″ = Ph). Moreover, cyclisation of the acetyl derivatives of hydroxy-esters of this type proceeds satisfactorily: ethyl α-acetoxy-α-methylpropionate (III; R = R′ = Me, R″ = H) gives a 46% yield of γγ-dimethyltetronic acid (IV; R = R′ = Me, R″ = H), and methyl acetoxydiphenylacetate (III; R = R′ = Ph, R″ = H) gives an 85% yield of γγ-diphenyltetronic acid (IV; R = R′ = Ph, R″ = H).

Surprisingly, the use of di*iso*propylaminomagnesium bromide to effect the cyclisation of methyl *o*-acetoxybenzoate to 4-hydroxycoumarin was much less effective than the use of sodium, only a 2% yield being obtained; methyl *o*-phenylacetoxybenzoate gave only 11% of 4-hydroxy-3-phenylcoumarin. The sole acidic product from ethyl phenylacetoxysuccinate with di*iso*propylaminomagnesium bromide was phenylacetic acid, and it is noteworthy that from the above cyclisation of methyl *o*-acetoxybenzoate a considerable amount of methyl salicylate was recovered together with unchanged starting material. It seems possible that ester cleavage competes with cyclisation.

Nevertheless, this internal cyclisation makes a very clean and convenient route for the preparation of some tetronic acids and we are now investigating its application to the synthesis of more complex tetronic acids.

Experimental

Ethyl α-(Ethoxycarbonylacetoxy)propionate (III; R = Me, R′ = H, R″ = CO_2Et).—Ethoxycarbonylacetyl chloride (43 g.) was added during 2 hr. to ethyl lactate (59 g.) in dry pyridine (100 c.c.) at 0°, and the mixture set aside overnight, then poured into water and extracted with ether. The ether extract was washed with aqueous sodium hydrogen carbonate, dilute sulphuric acid, and water, dried (Na_2SO_4), and evaporated. The residue gave *ethyl α-(ethoxycarbonylacetoxy)propionate* (29·6 g., 44%), b. p. 103—104°/0·1 mm., n_D^{14} 1·4310 (Found: C, 52·0; H, 6·8. $C_{10}H_{16}O_6$ requires C, 51·7; H, 6·9%).

Similarly were prepared:

Ethyl (phenylacetoxy)acetate (III; R = R′ = H, R″ = Ph) [from phenylacetyl chloride (131 g.) and ethyl glycollate (66·8 g.)] (75 g., 50%), b. p. 120°/0·05 mm., n_D^{14} 1·5017 (Found: C, 65·6; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·4%).

[3] Frostick and Hauser, *J. Amer. Chem. Soc.*, 1949, **71**, 1350.
[4] Royals and Turpin, *ibid.*, 1954, **76**, 5452.

Ethyl α-(phenylacetoxy)propionate (III; R = Me, R′ = H, R″ = Ph) [from phenylacetyl chloride (100 g.) and ethyl lactate (54 g.)] (73·1 g., 67%), b. p. 110°/0·2 mm., n_D^{14} 1·4917 (lit.,[5] b. p. 161°/13 mm., n_D^{19} 1·4904).

Ethyl α-phenyl-α-(phenylacetoxy)acetate (III; R″ = R′ = Ph, R = H) [from phenylacetyl chloride (110 g.) and ethyl mandelate (100 g.)] (125 g., 75%), b. p. 164—168°/0·1 mm., n_D^{18} 1·5397 (Found: C, 72·5; H, 5·8. $C_{18}H_{18}O_4$ requires C, 72·4; H, 6·1%) (the ester did not always distil satisfactorily in bulk).

Ethyl α-methyl-α-phenylacetoxypropionate (III; R = R′ = Me, R″ = Ph) [from phenylacetyl chloride (15·4 g.) and ethyl α-hydroxy-α-methylpropionate[6] (9·9 g.)] (10 g., 56%), b. p. 150°/7 mm., n_D^{18} 1·4886 (Found: C, 67·6; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·3%).

Ethyl (phenylacetoxy)succinate (III; R = CH_2·CO_2Et; R′ = H, R″ = Ph) [from phenylacetyl chloride (109 g.) and ethyl malate (95 g.)] (85 g., 55%), b. p. 153—160°/15 mm., n_D^{19} 1·4900 (Found: C, 62·4; H, 6·5. $C_{14}H_{20}O_6$ requires C, 62·3; H, 6·5%).

Cyclisations with Sodium.—α-Phenyltetronic acid (IV; R = R′ = H, R″ = Ph). A mixture of ethyl phenylacetoxyacetate (31·1 g.), sodium (3·0 g.), and toluene (50 g.) was heated to boiling. A brown solid separated as the sodium dissolved. The suspension was treated with hydrochloric acid, the toluene layer separated, and the aqueous layer extracted with ether and benzene. Solvents were evaporated from the combined dried (Na_2SO_4) extracts: recrystallisation of the residue from aqueous methanol gave α-phenyltetronic acid (5·0 g., 20%), m. p. 256—257° (lit.,[7] 254°) (Found: C, 68·2; H, 4·4. Calc. for $C_{10}H_8O_3$: C, 68·1; H, 4·6%).

γ-Methyl-α-phenyltetronic acid (IV; R = Me, R′ = H, R″ = Ph). A mixture of ethyl α-(phenylacetoxy)propionate (33·9 g.), sodium (3·0 g.), and toluene (45 ml.) was stirred vigorously and heated to the b. p.; reaction did not begin until the toluene was almost boiling but was then vigorous. After 15 min. the mixture was a thick brown syrup. This was treated as above, giving γ-methyl-α-phenyltetronic acid (8 g., 29%) which after drying at 100°/10 mm. for 6 hr. had m. p. 165°, resolidifying and then melting at 181—182° (lit.,[8] m. p. 178°).

αγ-Diphenyltetronic acid (IV; R = R″ = Ph, R′ = H). Ethyl α-phenyl-α-(phenylacetoxy)-acetate (15·4 g.) was treated with sodium (1·2 g.) in toluene (25 ml.) as described above. When the mixture was treated with acid, αγ-diphenyltetronic acid (4·6 g., 33%) separated. Recrystallised from aqueous ethanol it had m. p. 205—208° (lit.,[9] m. p. 209°).

γ-Methyltetronic acid (IV; R = Me, R′ = R″ = H). Ethyl α-(ethoxycarbonylacetoxy)-propionate (5·8 g.) was treated with sodium (0·6 g.) in toluene (25 ml.) as described above. The mixture was treated with hydrochloric acid (3 ml. of concentrated acid in 4 ml. of water), and the aqueous layer separated and extracted with ether. The ether extract was then extracted with aqueous sodium hydrogen carbonate, and the alkaline solution acidified with dilute sulphuric acid and extracted with ethyl acetate (continuous extraction). Evaporation of the ethyl acetate gave a dark brown oil (1·8 g.) which solidified. Recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave γ-methyltetronic acid, m. p. 115° (lit.,[10] m. p. 118°).

Cyclisations with Diisopropylaminomagnesium Bromide.—α-Phenyltetronic acid (IV; R = R′ = H, R″ = Ph). Ethyl (phenylacetoxy)acetate (26·0 g.) in dry ether (50 ml.) was added during 1 hr. to a stirred ethereal suspension of di*iso*propylaminomagnesium bromide [from magnesium (7·3 g.), ethyl bromide (33 g.), and then di*iso*propylamine (30·3 g.)]; a white solid separated. The mixture was stirred for a further ½ hr. with gentle warming. The orange mixture was poured on ice (200 g.) and hydrochloric acid (25 ml.). The aqueous layer was separated and extracted with ether, and the combined ether extracts were then extracted with aqueous sodium hydrogen carbonate. Acidification of the alkaline extract precipitated α-phenyltetronic acid (4·5 g., 21%), m. p. 259—261°.

γ-Methyl-α-phenyltetronic acid (IV; R = Me, R′ = H, R″ = Ph). Ethyl α-(phenylacetoxy)propionate (11·8 g.) was added during 1 hr. to an ethereal suspension of di*iso*propylaminomagnesium bromide [from magnesium (2·4 g.), ethyl bromide (10·9 g.), and di*iso*propylamine (10·1 g.)], and the mixture was refluxed ½ hr. and then kept overnight. Dilute hydrochloric acid (25 ml. of concentrated acid in 75 ml. of water) was added, and the aqueous layer separated and saturated with sodium chloride and extracted with ether. The combined extracts were extracted with aqueous sodium hydrogen carbonate; acidification then precipitated

[5] Kenyon, Phillips, and Turley, *J.*, 1925, **127**, 399.
[6] Hepworth, *J.*, 1919, **115**, 1203.
[7] Dimroth and Eble, *Ber.*, 1906, **39**, 3929.
[8] Dimroth and Feuchter, *Ber.*, 1903, **36**, 2255.
[9] Kohler, Petersen, and Bickel, *J. Amer. Chem. Soc.*, 1934, **56**, 2006.
[10] Benary, *Ber.*, 1911, **44**, 1759.

γ-methyl-α-phenyltetronic acid (5·9 g., 60%) which on recrystallisation from aqueous methanol had m. p. 165°, resolidifying and then melting at 180°.

αγ-Diphenyltetronic acid (R = R″ = Ph, R′ = H). Ethyl α-phenyl-α-(phenylacetoxy)-acetate (14·8 g.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·4 g.) by a similar procedure gave αγ-diphenyltetronic acid (7·3 g., 58%), m. p. 205—208° after recrystallisation from ethanol.

γγ-Dimethyltetronic acid (IV; R = R′ = Me, R″ = H). This was obtained from ethyl α-acetoxy-α-methylpropionate (12·0 g.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·4 g.). The final extraction of the acidified carbonate extract was with ethyl acetate by continuous extraction. γγ-Dimethyltetronic acid (4·1 g., 64%) had m. p. 140—142° (lit.,[11] m. p. 142°) after crystallisation from benzene.

γγ-Dimethyl-α-phenyltetronic acid (IV; R = R′ = Me, R″ = Ph). From ethyl α-methyl-α-(phenylacetoxy)propionate (3·7 g.) and di*iso*propylaminomagnesium bromide (from magnesium, 1·0 g.) gave this *acid* (1·95 g., 64%), m. p. 210—213° (from aqueous ethanol) (Found: C, 70·3; H, 5·9. $C_{13}H_{12}O_3$ requires C, 70·6; H, 5·9%).

γγ-Diphenyltetronic acid (IV; R = R′ = Ph, R″ = H). Obtained from methyl acetoxydiphenylacetate (14·2 g.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·4 g.), this acid (9·2 g., 85%) had m. p. 212° (from ethanol) (lit.,[12] m. p. 212°).

4-Hydroxycoumarin. Methyl *o*-acetoxybenzoate (19·4 g.) in ether (50 ml.) was added dropwise during 1¼ hr. to ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·43 g.). A vigorous reaction occurred during the addition and a brown solid separated. Isolation through aqueous sodium hydrogen carbonate as above gave 4-hydroxycoumarin (250 mg., 1·5%), m. p. 212° (lit.,[1b] m. p. 214—216°). Ether was evaporated from the carbonate-washed solution, and the oily residue dissolved in boiling light petroleum (b. p. 80—100°), which, on cooling, deposited colourless crystals (700 mg.), m. p. *ca.* 135°, which gave a purple colour with ferric chloride but were insoluble in aqueous sodium hydrogen carbonate. This product is being examined further. The residue (16·6 g.) from the light petroleum mother-liquors contained methyl *o*-acetoxybenzoate and methyl salicylate. Repetition of this experiment using only one-third of the quantity of methyl *o*-acetoxybenzoate gave virtually the same yield of 4-hydroxycoumarin.

4-Hydroxy-3-phenylcoumarin.—Prepared from methyl *o*-phenylacetoxybenzoate[1] (12·3 g., 0·05 mol.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·43 g., 0·1 mol.), 4-hydroxy-3-phenylcoumarin (1·18 g., 10·9%) had m. p. 234° (lit.,[1b] m. p. 234—235°).

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[*Received, April 16th*, 1956.]

[11] Benary, *Ber.*, 1907, **40**, 1079; Jones and Whiting, *J.*, 1949, 1419.
[12] Lecocq, *Compt. rend.*, 1946, **222**, 299.

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793. *The Preparation of 4-Amino- and Other Pteridines.**

By R. M. EVANS, P. G. JONES, P. J. PALMER, and F. F. STEPHENS.

An improved preparation of 4 : 5 : 6-triaminopyrimidine from 4 : 6-diaminopyrimidine-2-sulphinic acid and its condensation with glyoxal to give 4-aminopteridine are described. Several 2-substituted 4-amino- and 4-substituted 2-amino-pteridines have also been prepared.

A LARGE quantity of 4-aminopteridine was required and was prepared by condensation of 4 : 5 : 6-triaminopyrimidine with glyoxal.[1] If the pH of the reaction mixture is controlled, this condensation always proceeds satisfactorily, regardless of the age of the glyoxal.[1] Of the various routes available for the preparation of 4 : 5 : 6-triaminopyrimidine, oxidation of 4 : 5 : 6-triamino-2-mercaptopyrimidine to 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid and desulphination with mineral acid[2] proved most expedient for large-scale working.

* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[2] Hoffer, Jubilee Vol., Emil Barell, 1946, p. 428.

A great disadvantage of this route is the poor yield obtained in the reduction of 4 : 6-diamino-2-mercapto-5-nitrosopyrimidine to the 5-amino-compound. Since 4 : 6-diaminopyrimidine can be nitrated in high yield [3] to give 4 : 6-diamino-5-nitropyrimidine, which in turn has been reduced [4] to give 4 : 5 : 6-triaminopyrimidine, we examined the possibility of preparing 4 : 6-diaminopyrimidine by oxidation of the readily available 4 : 6-diamino-2-mercaptopyrimidine to the corresponding sulphinic acid and subsequent desulphination by mineral acid.[2] Further, 4 : 6-diaminopyrimidine is known to give a colour reaction with nitrous acid,[5] indicating the formation of a 5-nitroso-compound, so that an alternative route might become available for the triamine.

Oxidation of 4 : 6-diamino-2-mercaptopyrimidine by hydrogen peroxide gave the sulphinic acid in high yield, but no 4 : 6-diaminopyrimidine was at first isolated after refluxing the acid in N-sulphuric acid, although sulphur dioxide was liberated in the usual way. It was then found that dry alcoholic hydrogen chloride smoothly decomposed 4 : 6-diaminopyrimidine-2-sulphinic acid at room temperature, to give 4 : 6-diaminopyrimidine hydrochloride in good yield. As both 4 : 6-diaminopyrimidine and its hydrochloride are readily soluble in water, conversion of this desulphination product into its free base (for subsequent nitration) by ordinary chemical means was troublesome, but was most satisfactorily effected by passage down a column of Amberlite IRA-400 (OH) resin. The pyrimidine base was nitrated and reduced and gave 4 : 5 : 6-triaminopyrimidine in excellent yield. 4 : 6-Diamino-5-nitrosopyrimidine was prepared directly from 4 : 6-diaminopyrimidine hydrochloride by treatment of a hydrochloric acid solution of the latter with sodium nitrite, and with sodium dithionite gave the expected 4 : 5 : 6-triaminopyrimidine, though in lower overall yield than was obtained from the nitro-compound.

Since the nitration procedure was to be preferred, a further study of the acid desulphination of pyrimidine-2-sulphinic acids was made, with the object of avoiding the use of ion-exchange resins, and especially to discover why the 4 : 6-diamino-compound behaved differently from the 4 : 5 : 6-triamino-compound. The assumption was made that the mechanism of desulphination of 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid is (I) ⟶ (II) ⟶ (III). The 4-amino-group of 4 : 5-diaminopyrimidine being the more basic,[6] it would be expected that in acid solutions 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid would first accept a proton to give the resonance-stabilised cation (I) and that the acceptance of a second proton to give (II) would provide the necessary conditions for heterolytic cleavage of the C–S bond, yielding the ion (III), sulphur dioxide, and a proton. In acid solution, the ion (III) will then give the 4 : 5 : 6-triaminopyrimidine cation.

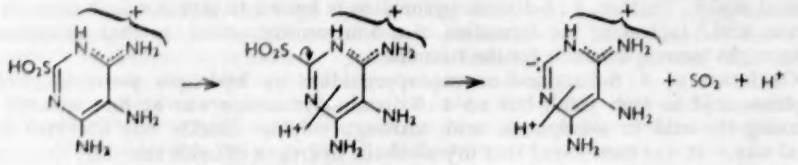
Although an amino-group in the 5-position of the pyrimidine nucleus has only feebly basic properties,[7] it seems reasonable to presume that the monocation (I) derived from 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid will more readily accept the second proton than will the monocation (IV) derived from 4 : 6-diaminopyrimidine 2-sulphinic acid, so that in the latter case desulphination occurs less readily. It follows therefore that, if on treatment of 4 : 6-diaminopyrimidine-2-sulphinic acid with boiling N-sulphuric acid the cation (IV) does not readily accept a second proton, cleavage of the C–S bond will be inhibited and decomposition may be expected to occur in the manner accepted for aromatic sulphinic acids : [8]

$$3R{\cdot}SO_2H \longrightarrow R{\cdot}SO_2{\cdot}SR + R{\cdot}SO_3H + H_2O$$

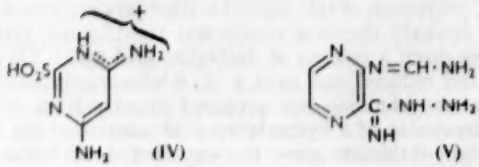
[mechanistically, this may proceed by disproportionation (cf. Kharasch [9])]. The pyrimidinesulphonic acid corresponding to $R{\cdot}SO_3H$ would be hydrolysed under these conditions [10] to 4 : 6-diamino-2-hydroxypyrimidine. There is the further possibility of radical decomposition. We may expect to find in this reaction, then, loss of sulphur dioxide and

[3] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 355.
[4] Robins, Dille, Willits, and Christensen, *J. Amer. Chem. Soc.*, 1953, **75**, 263.
[5] Lythgoe, Todd, and Topham, *J.*, 1944, 315.
[6] Gabriel and Colman, *Ber.*, 1899, **32**, 2929; Forrest and Walker, *J.*, 1949, 79.
[7] Whittaker, *J.*, 1951, 1565.
[8] Otto, *Ber.*, 1876, **9**, 1639; Pauly and Otto, *Ber.*, 1877, **10**, 2181; 1878, **11**, 2070, 2073; von Braun and Weissbach, *Ber.*, 1930, **63**, 2836.
[9] Kharasch, *Chem. Rev.*, 1946, **39**, 269.
[10] Greenbaum and Holmes, *J. Amer. Chem. Soc.*, 1954, **76**, 2899.

the formation of 4 : 6-diaminopyrimidine, 4 : 6-diamino-2-hydroxypyrimidine, and some complex compounds of the disulphoxide type. A closer experimental examination of this reaction proved this to be so, for 4 : 6-diaminopyrimidine and 4 : 6-diamino-2-hydroxypyrimidine were isolated and identified; a compound agreeing in composition with that of the disulphoxide type was isolated, but its constitution was not rigidly established.



(I) (II) (III)



(IV) (V)

If on the other hand the acid strength of the medium for the desulphination of 4 : 6-diaminopyrimidine-2-sulphinic acid is increased, the monocation (IV) may be forced to accept a second proton and normal desulphination should occur. By decomposing the sulphinic acid with 20N-sulphuric acid in the cold, quantitative conversion into 4 : 6-diaminopyrimidine sulphate was achieved; this sulphate could be nitrated without conversion into the free base. Similarly, 20N-sulphuric acid may be used to convert 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid into 4 : 5 : 6-triaminopyrimidine sulphate. Concentrated hydrochloric acid also converted 4 : 6-diaminopyrimidine-2-sulphinic acid into 4 : 6-diaminopyrimidine hydrochloride in high yield. These reactions are extremely rapid and the isolated compounds are free from by-products.

4 : 6-Diamino-5-nitropyrimidine was satisfactorily reduced with hydrogen and Raney nickel or sodium dithionite or iron and hydrochloric acid. The overall yield of 4-aminopteridine by the route outlined was greater than 30%.

When heated with aqueous ammonia to 170° 4-aminopteridine was quantitatively converted into ammonium 2-aminopyrazine-3-carboxylate (cf. Taylor [11]). Heating the pteridine with hydrazine led to a crystalline compound giving the analytical figures for 2-amidrazono-3-formamidinopyrazine (V). It was also noted that 4-aminopteridine formed a complex with oxalic acid from which the base could be regenerated by action of ammonia.

Interest in the biological properties of 4-aminopteridine lead to the preparation of many other pteridines; these were synthesised by conventional methods,[12] and preparations of some of the new compounds are reported in the Experimental section.

Experimental

N.B.: Difficulty was encountered in obtaining good analytical results for some of the compounds prepared, in spite of repeated crystallisations.[13]

The term " spirit " in the text refers to industrial methylated spirits.

4 : 5 : 6-Triaminopyrimidine-2-sulphinic Acid.—4 : 5 : 6-Triamino-2-mercaptopyrimidine sulphate (174 g.) was dissolved in 2N-sodium hydroxide (1070 ml.) and cooled to <10°.

[11] Taylor, Ciba Foundation Symposium, " The Chemistry and Biology of Pteridines," Churchill Ltd., London, 1954, p. 2.
[12] Albert, *Quart. Rev.*, 1952, **6**, 197.

6% Hydrogen peroxide (696 ml.) was slowly added with stirring so that the temperature did not exceed 20° (ice-water cooling) during 45 min.; stirring was continued for a further 30 min. and the mixture filtered. Acidification of the filtrate with glacial acetic acid (100 ml.) precipitated the sulphinic acid which was washed with water, then methanol, and air-dried, to give an off-white friable powder (98 g., 85%) identical with that described by Hoffer.[2] If a precipitate does not appear during the oxidation, the sulphinic acid must be purified by dissolving it in 3% ammonia solution (860 ml.), filtering from insoluble impurity, and reprecipitation with acetic acid; the yield is the same as above.

4 : 5 : 6-*Triaminopyrimidine Sulphate.*—*Hoffer's procedure.*[2] 4 : 5 : 6-Triaminopyrimidine-2-sulphinic acid (50 g.) was boiled under reflux in N-sulphuric acid (1100 ml.) for 2 hr., by which time evolution of sulphur dioxide had ceased. The hot solution was filtered from a little sulphur, and the filtrate cooled to 0° overnight. The crystalline product was removed, washed with a little cold water, then methanol and finally with ether, and air-dried to give crude 4 : 5 : 6-triaminopyrimidine sulphate (46 g.). The material was purified by heating it to incipient boiling with water (460 ml.) and ammonia (46 ml.; *d* 0·880), cooling to room temperature, removing the insoluble impurity, and reprecipitating the sulphate by addition of 50% v/v sulphuric acid (20 ml.). In this way, almost white 4 : 5 : 6-triaminopyrimidine sulphate (40 g.) was obtained. Recrystallisation from water gave white plates (Found : C, 20·4; H, 4·95; N, 29·05. Calc. for $C_4H_7N_5,H_2SO_4,H_2O$: C, 19·9; H, 4·6; N, 29·05%). Cf. also p. 4110.

4-*Aminopteridine.*—4 : 5 : 6-Triaminopyrimidine sulphate (50 g.) was dissolved in N-sodium hydroxide (415 ml.) at 70—75°. The pH of this solution should be 9·5—10·5. To the solution of the base was added a solution of glyoxal (25 g. of commercial 50% material) in water (250 ml.) at 70—75° with stirring and the mixture was placed on a steam-bath for 1 hr. After cooling to 0°, the crude 4-aminopteridine was removed, washed with water, and crystallised from 100 parts of water (charcoal) to give an off-white product (20 g.) m. p. 309—311° (decomp.) (ultraviolet absorption spectra in neutral and acid solution were identical with those described by Albert, Brown, and Cheeseman.[1] Infrared absorption, Nujol mull, gave peaks at 3400, 3180, 1658, 1580, 1550, and 1520 cm.$^{-1}$) (Found : C, 49·5; H, 3·4; N, 47·6. Calc. for $C_6H_5N_5$: C, 49·0; H, 3·4; N, 47·5%). The following figures give the yields of crude 4-aminopteridine, in parentheses, when the condensation was done at different pH : pH 11·9 (49·2%); pH 10·5 (79·5%); pH 7·2 (33·6%); pH 6·9 (61·5%).

4-Aminopteridine (1 g.) was dissolved in warm N-oxalic acid (27·2 ml.) and filtered and the filtrate allowed to cool, to give a granular *oxalate* (1·35 g.) which crystallised from water [Found : C, 43·6; H, 3·8; N, 39·9. $(C_6H_5N_5)_2,(CO_2H)_2$ requires C, 43·75; H, 3·15; N, 36·5%].

4 : 6-*Diaminopyrimidine-2-sulphinic Acid.*—To a solution of 4 : 6-diamino-2-mercaptopyrimidine (50 g.) in 2N-sodium hydroxide (220 ml.) was added 3% hydrogen peroxide solution (750 ml.) at <20° (cooling). Stirring was continued for a further 30 min. and the clear pale yellow solution acidified with acetic acid (*ca.* 50 ml.). The precipitate was washed with water, methanol, and then ether and air-dried, to give an off-white amorphous *acid* (58 g., 95%), m. p. 168—170° (decomp.). For analysis, a sample was dissolved in dilute aqueous ammonia and reprecipitated with acetic acid (Found : C, 27·8; H, 3·8; N, 32·1. $C_4H_4O_2N_4S$ requires C, 27·6; H, 3·5; N, 32·2%). The above oxidation, on 100 g. scale, gave a 98% yield.

4 : 6-*Diaminopyrimidine Hydrochloride.*—(*a*) 4 : 6-Diaminopyrimidine-2-sulphinic acid (50 g.) was shaken for 30 min. in dry ethanol (500 ml.) containing dry 2·5N-ethanolic hydrogen chloride (150 ml.). The mixture was cooled to 0° and after 1 hr. the crystals were removed, washed with ether, and dried to give pale yellow needles (23 g.), m. p. 196—198°. Concentration of the original filtrate to 250 ml., followed by addition of ether (750 ml.), gave a further crop of almost white needles (15 g.), m. p. 188°. Recrystallisation from spirit gave white needles, m. p. 203—204° identical with a specimen of hydrochloride prepared from authentic 4 : 6-diaminopyrimidine (Found : C, 33·3; H, 4·8; N, 38·1; Cl, 24·1. $C_4H_6N_4,HCl$ requires C, 32·8; H, 4·8; N, 3·82; Cl, 24·2%). Ultraviolet absorption max. in EtOH : 221 (ε 24,500) and 265 mμ (ε 1167).

(*b*) The sulphinic acid (5 g.) was added portion-wise to hydrochloric acid (15 ml.; *d* 1·18) at room temperature. The reaction was vigorous and sulphur dioxide was freely evolved. Hydrochloric acid was removed from the resulting slurry under reduced pressure, and the residue washed with acetone, then ether, to give 4 : 6-diaminopyrimidine hydrochloride (4·05 g.), m. p. 195°. Recrystallisation of a sample from spirit raised the m. p. to 201—202° (undepressed when mixed with an authentic sample).

4 : 6-*Diaminopyrimidine.*—A solution of 4 : 6-diaminopyrimidine hydrochloride (38 g.) in water (380 ml.) was allowed to percolate through a column of Amberlite IRA-400 (OH) resin (150 g.), and the column eluted with water (6 l.). As the eluate was found to have a pH of 5 it

was again allowed to percolate through the regenerated column. Removal of the water from the second eluate gave 4 : 6-diaminopyrimidine (26 g.) as colourless needles, m. p. 273—274°.

Desulphination of 4 : 6-*Diaminopyrimidine-2-sulphinic acid with* N-*Sulphuric Acid.*—4 : 6-Diaminopyrimidine-2-sulphinic acid (10 g.) was boiled under reflux with N-sulphuric acid (230 ml.) for 1 hr., the clear solution was treated with charcoal and filtered, and the filtrate cooled to 0° for 24 hr. The precipitate was washed and dried, to give colourless needles of 4 : 6-diamino-2-hydroxypyrimidine sulphate (4·65 g.) (Found: C, 25·05; H, 4·9; N, 28·55; S, 8·5. Calc. for $C_4H_6ON_4,\frac{1}{2}H_2SO_4,H_2O$: C, 24·9; H, 4·7; N, 29·0; S, 8·3%). The infrared spectrum of this compound was identical with that of 4 : 6-diamino-2-hydroxypyrimidine sulphate prepared from authentic 4 : 6-diamino-2-hydroxypyrimidine.[13]

The original filtrate from the above preparation was heated to boiling and treated with barium hydroxide (36·2 g. of octahydrate) in hot water (50 ml.). After filtration and washing of the barium sulphate, the filtrate was cooled and saturated with carbon dioxide to precipitate barium carbonate. This was removed and the filtrate evaporated to dryness at reduced pressure to a white solid residue (3·67 g.). Extraction of the residue with boiling spirit gave, after concentration, colourless needles (1·12 g.) of 4 : 6-diaminopyrimidine, m. p. and mixed m. p. 274—275°. The spirit-insoluble residue (0·73 g.) crystallised from water as a white *substance*, m. p. <330° (Found: C, 29·3; H, 4·0; N, 34·1. $C_8H_{10}O_2N_6S_2,H_2O$ requires C, 28·9; H, 3·6; N, 33·7%). A similar product was obtained on reaction of the sulphinic acid with Amberlite IR-120 (H) in water at 80°.

4 : 6-*Diaminopyrimidine Sulphate.*—(a) *Reference compound.* 4 : 6-Diamino-2-mercaptopyrimidine (30 g.) was desulphurised by Brown's method [3] to give 4 : 6-diaminopyrimidine (15·7 g.), m. p. 267—268°. This material (1 g.) was dissolved in sulphuric acid (2 ml.; *d* 1·84) with cooling and the clear solution poured into excess of spirit, to precipitate 4 : 6-*diaminopyrimidine sulphate*, m. p. 181—185° (decomp.) (Found: C, 21·4; H, 3·65; N, 25·2. $C_4H_6N_4,H_2SO_4,H_2O$ requires C, 21·2; H, 4·5; N, 24·7%). Repeated recrystallisation of this sulphate from aqueous alcohol gave another stable *sulphate*, m. p. 247° (decomp.), containing only half a mol. of sulphuric acid (Found: C, 27·25; H, 5·0; N, 32·2. $C_4H_6N_4,\frac{1}{2}H_2SO_4,H_2O$ requires C, 27·1; H, 5·1; N, 31·6%).

(b) *By desulphination.* 4 : 6-Diaminopyrimidine-2-sulphinic acid (9 g.) was added to 20N-sulphuric acid (36 ml.) with stirring at room temperature. The mixture evolved sulphur dioxide and thickened. When addition was complete, the mixture was heated to 90°, then cooled, and acetone added to give a total volume of 250 ml. The precipitated sulphate was removed, washed with acetone, then ether, and dried to give off-white crystals (11·5 g., 98%), m. p. 183—184°.

4 : 5 : 6-*Triaminopyrimidine Sulphate.*—(a) *Iron–hydrochloric acid reduction.* The *wet* 4 : 6-diamino-5-nitropyrimidine obtained by nitration of 4 : 6-diaminopyrimidine (25 g.; Brown [3]) was suspended in water (1600 ml.), iron reduced by hydrogen (32 g.), and concentrated hydrochloric acid (2 ml.) were added, and the mixture was heated on a boiling-water bath for 2½ hr. with vigorous stirring. The mixture was filtered, and the filtrate acidified with 50% v/v sulphuric acid (160 ml.), and cooled to give 4 : 5 : 6-triaminopyrimidine sulphate (41 g.).

(b) *Sodium dithionite reduction.* Finely ground 4 : 6-diamino-5-nitropyrimidine (7·5 g.) was suspended in water (150 ml.) at 80° and sodium dithionite (37·5 g.) added with vigorous stirring. After 10 min., the mixture was gently boiled for 5 min., then filtered to remove unchanged nitrocompound (0·3 g.). Acidification of the filtrate with 50% v/v sulphuric acid (75 ml.) gave 4 : 5 : 6-triaminopyrimidine sulphate (7·7 g.); a further quantity (1·3 g.) was obtained from the mother-liquors after boiling to remove sulphur dioxide. Recrystallisation of the combined products from dilute sulphuric acid gave white plates (7·73 g.) of 4 : 5 : 6-triaminopyrimidine sulphate.

(c) *By desulphination.* 4 : 5 : 6-Triaminopyrimidine-2-sulphinic acid (9 g.) was added to 20N-sulphuric acid (36 ml.). After cooling, acetone (200 ml.) was added and the white solid (12·4 g.) removed. Recrystallisation from water (100 ml.) containing 2N-sulphuric acid (25 ml.) gave white plates of 4 : 5 : 6-triaminopyrimidine sulphate (8·2 g.).

4 : 6-*Diamino-5-nitrosopyrimidine.*—A solution of 4 : 6-diaminopyrimidine hydrochloride (2 g.) in N-hydrochloric acid (48 ml.) was cooled to between 0° and −5°. Sodium nitrite (1·41 g.) in water (15 ml.) was added during 20 min. with cooling to <0°. The solution was stirred for a further hour, whilst being allowed to come to room temperature, before addition of solid sodium hydrogen carbonate to pH 8. The light blue, solid *nitroso-compound* was filtered off, washed with cold water, and reduced without drying. A sample for analysis was obtained as

[13] Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3112.

fine blue plates from water (Found : C, 34·7; H, 3·6; N, 50·9. $C_4H_5ON_5$ requires C, 34·5; H, 3·6; N, 50·35%).

The moist nitroso-compound was suspended in water (20 ml.) at 60°, and sodium dithionite (5 g.) added portionwise, giving a clear orange solution. This was heated to the b. p., acidified with 50% v/v sulphuric acid (15 ml.), boiled for a few minutes, and cooled to room temperature. The precipitated solid was removed, washed with water, spirit, and ether, and dried to give **4 : 5 : 6**-triaminopyrimidine sulphate as pale yellow needles (1·8 g.).

2-Aminopyrazine-3-carboxylic Acid.—4-Aminopteridine (20 g.), ammonia (400 ml.; *d* 0·88), and water (600 ml.) were heated together in an autoclave at 165—170° for 1 hr., then allowed to cool overnight. The resulting solution was evaporated to dryness under reduced pressure to give a bright yellow solid (21·6 g.), m. p. 226° (decomp.). Crystallisation from 50% aqueous acetone gave pale yellow needles of ammonium 2-aminopyrazine-3-carboxylate, m. p. 232° (decomp.) (Found : C, 38·9; H, 5·1; N, 36·5. $C_5H_8O_2N_4$ requires C, 38·5; H, 5·2; N, 35·9%). Ultraviolet absorption max. in H_2O : 242 (ε 10,050) and 340 mμ (ε 6020). A solution of this salt in water, adjusted to pH 2·5 by addition of hydrochloric acid, gave needles of 2-aminopyrazine-3-carboxylic acid, m. p. 203—204° (decomp.), identical (infrared comparison) with a specimen prepared by the method of Weijlard, Tishler, and Erickson.[14]

Action of Hydrazine on 4-Aminopteridine.—4-Aminopteridine (0·27 g.) was refluxed for 10 min. in 90% hydrazine hydrate (5 ml.), forming a deep red solution. After cooling, the solution was diluted with water and extracted with ethyl acetate, evaporation of which gave pale yellow crystals, m. p. 170—172°. Recrystallisation from *cyclo*hexane–ethanol gave *2-amidrazono-2-formamidinopyrazine* as yellow needles, m. p. 173—174° (Found : C, 40·4; H, 4·9; N, 54·3. $C_6H_9N_7$ requires C, 40·2; H, 5·1; N, 54·7%).

4-Amino-2-methylpteridine.—**4 : 5 : 6**-Triamino-2-methylpyrimidine [5] (3 g.) was dissolved in boiling 2N-sulphuric acid (25 ml.), and the solution cooled to give the crystalline sulphate. After being washed with acetone and air-dried, the sulphate was dissolved in N-sodium hydroxide (40 ml.) at 70—75° and the pH of the solution adjusted, if necessary to 9—10. Glyoxal (2 g.; 50% commercial syrup) in water (20 ml.) at 75° was added and the mixture was allowed to cool to room temperature; the crude *pteridine* was removed, crystallised from water (charcoal), and dried to give off-white needles (2·4 g.), m. p. 234—235° (Found : C, 52·3; H, 4·2. $C_7H_7N_5$ requires C, 52·2; H, 4·4%). Ultraviolet absorption max. in EtOH : 247 (ε 13,800) and 340 mμ (ε 4880).

2-Substituted **4 : 6**-*Diamino-5-phenylazopyrimidines.*—The compounds in Table 1 were prepared by condensation of the appropriate amidine hydrochloride with phenylazomalononitrile by the method of Lythgoe, Todd, and Topham.[5]

TABLE 1. *2-Substituted* **4 : 6**-*diamino-5-phenylazopyrimidines.*

2-Subst.	M. p.	Colour	Solvent for recryst.	Yield * (%)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Et	263—264°	Orange	Ethanol	23	59·3	6·0	$C_{12}H_{14}N_8$	59·5	5·8
Pr^n	255—256	Light brown	,,	45	60·6	6·2	$C_{13}H_{16}N_8$	60·9	6·3
Bu^n	262	Golden	Spirit	33	61·5	6·3	$C_{14}H_{16}N_8$	62·2	6·7
Bu^i	260—261	Golden-yellow	,,	47	62·6	6·6	$C_{14}H_{16}N_8$	62·2	6·7
Ph	294—295	Orange	Pyridine	67	66·3	5·0	$C_{16}H_{14}N_8$	66·2	4·9
CH_2Ph	275	Orange	,,	55	66·7	5·2	$C_{17}H_{16}N_8$	67·1	5·3
p-Cl·C_6H_4·CH_2	277	Orange	Et acetate	70	60·4	4·6	$C_{17}H_{15}N_8Cl$	60·3	4·5
p-C_6H_4Me ...	306—307	Red	Pyridine	80	67·0	5·5	$C_{17}H_{16}N_8$	67·1	5·3

* Based on the substituted amidines.

2-Substituted **4 : 5 : 6**-*Triaminopyrimidines.*—The compounds in Table 2 were prepared by reduction of the preceding azo-compounds.

2-Substituted **4**-*Aminopteridines.*—Condensation of the above triaminopyrimidines with glyoxal in the manner already described gave the 2-substituted 4-aminopteridines described in Table 3.

4-Amino-2-methoxypteridine.—**4 : 6**-Diamino-2-chloro-5-nitropyrimidine (1·5 g.), methanol (60 ml.), and potassium hydroxide (1·5 g.) were boiled under reflux for 30 min.; after cooling, the cream-coloured solid was removed, washed with water, then methanol, and dried to give a crystalline product, m. p. 263° (1·05 g.). This product (1·0 g.) was suspended in dry ethanol (150 ml.) and reduced with hydrogen at 40—50°/50 atm. in presence of Raney nickel for 12 hr.

[14] Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802.

After removal of catalyst from the hot mixture, the filtrate was concentrated to small bulk (25 ml.) and the dark solution boiled with charcoal and filtered. The filtrate was boiled with 50% glyoxal (0·63 g.) in water (10 ml.) for ½ hr., then evaporated under vacuum, and the residue crystallised from spirit (charcoal) to give *4-amino-2-methoxypteridine* (0·25 g.), m. p. 222—225°. From spirit this formed very pale yellow crystals (0·16 g.), m. p. 224—225° (Found: C, 47·6; H, 4·2; N, 40·1. $C_7H_7ON_5$ requires C, 47·5; H, 4·0; N, 39·6%).

4-Amino-2-di-n-butylaminopteridine.—4 : 6-Diamino-2-chloro-5-nitropyrimidine (0·5 g.), di-*n*-butylamine (1 ml.), and dry ethanol (5 ml.) were refluxed for 3 hr. After cooling, the mixture was diluted with ether and filtered from a little starting material, and the filtrate washed with water. The ether solution was dried ($MgSO_4$), then evaporated to an orange gum which with

TABLE 2. *2-Substituted 4 : 5 : 6-triaminopyrimidines.*

2-Subst.	M. p.	Solvent [a]	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	Redn.[b]
Et	272°	H_2O	87	46·5	7·2	45·3	$C_6H_{11}N_5$	47·0	7·2	45·7	1
Pr[n]	171—172	CH	90	50·4	7·9	41·1	$C_7H_{13}N_5$	50·3	7·8	41·9	2
Bu[n]	151—152	EtOH–CH	90	52·8	8·6	38·9	$C_8H_{15}N_5$	53·0	8·3	38·6	2
Bu[i]	176	C_6H_6	75	52·7	8·3	—	$C_8H_{15}N_5$	53·0	8·3	—	2
Ph	189—190	H_2O	64	[c]	[c]	35·4	$C_{10}H_{11}N_5$	—	—	34·8	3
CH_2Ph	223—224	,,	62	60·7	6·05	33·4	$C_{11}H_{13}N_5$	61·4	6·1	32·5	3
p-Cl·C_6H_4·CH_2	244—245	,,	90	53·3	4·9	—	$C_{11}H_{12}N_5Cl$	52·9	4·85	—	4
p-C_6H_4Me ...	210—211	,,	53	61·9	6·3	—	$C_{11}H_{13}N_5$	61·4	6·1	—	3

[a] CH = *cyclo*hexane. [b] Methods of reduction: 1, Hydrogen and Adams catalyst at room temperature and atmospheric pressure in ethanol. 2, Hydrogen and Raney nickel at 100°/70 atm. in ethanol. 3, Zinc and acetic acid.[13] 4, Palladium–charcoal–hydrogen in formic acid (Davoll and Lowy, *J. Amer. Chem. Soc.*, 1952, **74**, 1563). [c] *Sulphate*, m. p. 238—242° (Found: N, 21·7. $C_{10}H_{11}N_5,H_2SO_4,H_2O$ requires N, 22·1%).

TABLE 3. *2-Substituted 4-aminopteridines.*

No.	2-Subst.	M. p.	Solvent [a]	Yield (%)	Ultraviolet spectrum max. (mμ)	ε	Solvent
1	Et	170°	C_6H_6	55 [c]	245, 336	16,900, 5880	H_2O
2	Pr[n]	145—146	,,	49	247, 335	17,900, 5920	EtOH
3	Bu[n]	136—137	C_6H_6–CH	44	247, 340	20,600, 6550	,,
4	Bu[i]	156	C_6H_6	44	247, 339	19,000, 5540	,,
5	Ph	240—241	H_2O	38 [d]	204, 271, 342	21,200, 19,700 6850	H_2O
6	CH_2Ph	188—189	[b]	63 [e]	247, 337	19,000, 5780	EtOH
7	*p*-Cl·C_6H_4·CH_2	185—186	[b]	17	248, 335	21,700, 6450	,,
8	*p*-C_6H_4Me	269—270	Spirit	58	204, 254, 285, 349	25,900, 13,650, 28,400, 8800	,,

No.	Found (%) C	H	N	Formula	Required (%) C	H	N
1	55·3	5·2	39·85	$C_8H_9N_5$	54·8	5·2	40·0
2	57·4	5·9	36·7	$C_9H_{11}N_5$	57·1	5·9	37·0
3	59·4	6·6	34·45	$C_{11}H_{13}N_5$	59·1	6·45	34·5
4	59·1	6·2	32·9	$C_{11}H_{13}N_5$	59·1	6·45	34·5
5	64·9	4·3	—	$C_{12}H_9N_5$	64·6	4·1	—
6	—	—	29·7	$C_{13}H_{11}N_5$	—	—	29·5
7	57·9	3·6	24·8	$C_{12}H_{10}N_5Cl$	57·5	3·7	25·8
8	66·0	4·75	30·5	$C_{12}H_{11}N_5$	65·8	4·7	29·5

[a] CH = *cyclo*Hexane. [b] Purified by dissolution in 0·5N-HCl and repptn. by aq. NH_3. [c–e] Material of m. p. (*c*) 155—160°, (*d*) 235—236°, (*e*) 183—185°.

light petroleum (b. p. 40—60°) gave pale yellow needles (0·35 g.), m. p. 88—90°. The product (0·35 g.) was reduced in methanol (20 ml.) by hydrogen and Adams catalyst at room temperature and pressure. After removal of the catalyst, the colourless solution rapidly became orange-yellow, and 50% glyoxal (0·15 g.) in water (10 ml.) was added. The solution was refluxed for 1½ hr., then evaporated, and the residue extracted with ethyl acetate. Evaporation of the ethyl acetate gave a gum which was chromatographed in benzene on acid-washed alumina. Elution with light petroleum–benzene (1 : 9) and evaporation of the eluate gave bright yellow

crystals (0·13 g.), m. p. 110—112°. Recrystallisation from aqueous spirit gave *4-amino-2-di-n-butylaminopteridine* as pale yellow needles, m. p. 110—112° (Found: C, 60·9; H, 7·7; N, 30·9. $C_{14}H_{22}N_6$ requires C, 61·4; H, 8·0; N, 30·6%).

2-Amino-4-methylpteridine.—2 : 4 : 5-Triamino-6-methylpyrimidine [15] (1 g.) was refluxed with a solution of glyoxal sodium hydrogen sulphite (2·24 g.) in water (22 ml.) for 80 min. The hot solution was filtered and the filtrate cooled, giving a brown solid. After being washed with alcohol the solid was shaken with N-sodium hydroxide (16 ml.) for 30 min., then filtered off, washed with water, and crystallised from water. *2-Amino-4-methylpteridine* (0·35 g.) separated as small yellow needles, slow decomp. from 290° (Found: C, 52·3; H, 4·3; N, 44·1. $C_7H_7N_5$ requires C, 52·2; H, 4·4; N, 43·5%). Ultraviolet absorption max. in H_2O: 226 (ε 28,000), 260 (ε 7800), and 368 mμ (ε 7100).

4-Alkyluracils.—The following compounds were prepared from the appropriate 2-thiouracils (cf. Anderson, Halverstadt, Miller, and Roblin [16]) by Brown's method [17] (yields are in parentheses): 4-Ethyluracil, (90%), m. p. 201—203°; Robinson and Tomlinson [18] give m. p. 205°. 4-n-*Propyluracil* (81%), colourless needles (from water), m. p. 217—219° (Found: C, 54·6; H, 6·4. $C_7H_{10}O_2N_2$ requires C, 54·5; H, 6·5%). 4-iso*Propyluracil* (71%), colourless plates (from water), m. p. 199—200° (Found: N, 18·4. $C_7H_{10}O_2N_2$ requires N, 18·2%).

6-Alkyl-2 : 4-diamino-5-nitropyrimidines.—Nitration of the appropriate uracil according to Gabriel and Colman's method [19] followed by treatment with phosphorus oxychloride and diethylaniline [20] and amination in phenol [21] gave the following compounds: *2 : 4-Diamino-6-ethyl-5-nitropyrimidine* (35%), yellow rhombs (from alcohol), m. p. (double) 179° and 191° (Found: C, 39·1; H, 5·0; N, 38·0. $C_6H_9O_2N_5$ requires C, 39·3; H, 4·95; N, 38·2%). *2 : 4-Diamino-5-nitro-6-n-propylpyrimidine* (29%), pale yellow plates (from alcohol), m. p. 162—164° (Found: C, 42·9; H, 5·55; N, 36·1. $C_7H_{11}O_2N_5$ requires C, 42·6; H, 5·6; N, 35·5%). *2 : 4-Diamino-5-nitro-6-isopropylpyrimidine* (24%), rhombs (from alcohol), m. p. 152—154° (Found: C, 42·3; H, 5·45; N, 35·3%).

6-Alkyl-2 : 4 : 5-triaminopyrimidines.—Hydrogenation of the nitropyrimidines in methanol with Raney nickel [22] gave *2 : 4 : 5-triamino-6-ethylpyrimidine* (57%), pale yellow prisms (from methanol), m. p. 244—248° (Found: C, 46·9; H, 7·3; N, 44·8. $C_6H_{11}N_5$ requires C, 47·0; H, 7·2; N, 45·7%), *2 : 4 : 5-triamino-6-n-propylpyrimidine* (77%), colourless rhombs (from ethanol), m. p. 183—186° (Found: C, 50·55; H, 7·6; N, 40·7. $C_7H_{13}N_5$ requires C, 50·3; H, 7·8; N, 41·9%), and 2 : 4 : 5-triamino-6-*iso*propylpyrimidine (91%), a pale blue unstable solid, m. p. 158—160°.

4-Alkyl-2-aminopteridines.—Condensation of the appropriate triaminopyrimidine with glyoxal sodium hydrogen sulphite as described for 2-amino-4-methylpteridine gave the following compounds: *2-Amino-4-ethylpteridine* (4%), long orange needles (from water), m. p. 186—188° (Found: C, 54·6; H, 5·3; N, 40·5. $C_8H_9N_5$ requires C, 54·8; H, 5·2; N, 40·0%). Ultraviolet absorption max. in H_2O: 226 (ε 26,700), 259 (ε 7300), and 369 mμ (ε 7150). *2-Amino-4-n-propylpteridine* (40%), pale brown plates (from ethanol), m. p. 183—184° (Found: C, 56·8; H, 5·6; N, 35·1. $C_9H_{11}N_5$ requires C, 57·1; H, 5·9; N, 37·0%). Ultraviolet absorption max. in H_2O: 227 (ε 24,100), 260 (ε 6000), and 368 mμ (ε 5400). *2-Amino-4-isopropylpteridine* (62%), fine yellow needles (from water), m. p. 162—164° (Found: C, 57·1; H, 5·7; N, 37·45%). Ultraviolet absorption max. in H_2O: 226 (ε 21,000), 259 (ε 6700), and 368 mμ (ε 5800).

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794. *Potential Thiophen Chemotherapeutics. Part V.* Preparation and Proof of Structure of Some Substituted 5-Aminothiophen-2-sulphonamides.†*

By J. Cymerman-Craig, G. N. Vaughan, and W. K. Warburton.

Nitration of methyl 2-thienyl sulphide gave the 5-nitro-compound, converted into methyl 5-phthalimido-2-thienyl sulphone. The unstable 5-*o*-carboxybenzamidothiophen-2-sulphinic acid lost sulphur dioxide and could not be transformed into the methyl sulphone.

Pure 5-nitrothiophen-2-sulphonyl chloride has been obtained by nitration of thiophen-2-sulphonyl chloride (improved preparation) and converted into 5-phthalimidothiophen-2-sulphonamide, which was opened to the phthalamic acid. Analogous reactions led to *N*-(5-sulphonamido-2-thienyl)succinamic acid, also obtained from 5-nitrothiophen-2-sulphonamide. The 2 : 5-orientation has been rigidly established for all these compounds.

In work on the synthesis of 5-aminothiophen-2-sulphonamide, the thiophen isostere of sulphanilamide, some thiophen compounds related to "Succinylsulphathiazole" 2-*p*-β-carboxypropionamidobenzenesulphonamidothiazole) and its phthaloyl analogue have been prepared.

Rigid proof of the 2 : 5-orientation was attempted by the preparation of methyl 5-phthalimido-2-thienyl sulphone independently from 2-nitrothiophen and methyl 2-thienyl sulphide.

Although potassiocarbazole condenses with, *e.g.*, *p*-bromochlorobenzene,[1] the more weakly basic potassiophthalimide did not react with 2-bromo- or 2-iodo-thiophen,[2] or with the activated 5-iodo-2-thienyl methyl sulphone [2] in dimethylformamide, with or without a copper catalyst, and attempted condensation with *o*- or *p*-chloronitrobenzene failed even at 200°.

Methyl 2-thienyl sulphide and acetyl nitrate (cf. Rinkes [3]) gave methyl 5-nitro-2-thienyl sulphide, and thence the sulphone, reduction of which in presence of phthalic anhydride afforded methyl 5-phthalimido-2-thienyl sulphone; this was converted into *N*-(5-methylsulphonyl-2-thienyl)phthalamic acid by sodium hydrogen carbonate.

2-Phthalimidothiophen was prepared by direct treatment of 2-thienylammonium chlorostannate with sodium acetate, acetic acid, and phthalic anhydride without isolation of the unstable 2-aminothiophen.

Reduction of 5-phthalimidothiophen-2-sulphonyl chloride was accompanied by ring-opening, giving 5-*o*-carboxybenzamidothiophen-2-sulphinic acid. This was exceedingly unstable, losing sulphur dioxide at room temperature (half-life *ca.* 90 min.) to give *N*-2-thienylphthalamic acid, also obtained on drying *in vacuo* at room temperature for 10 min. or on attempted recrystallisation.

Attempted alkylation of the disodium salt of 5-*o*-carboxybenzamidothiophen-2-sulphinic acid with methyl iodide or sulphate [4] was unsuccessful, and treatment of the silver salt with methyl iodide led only to methyl *N*-2-thienylphthalamate. No identifiable product was obtained from 5-*o*-carboxybenzamidothiophen-2-sulphinic acid and diazomethane.

Reduction of 5-phthalimidothiophen-2-sulphonyl chloride with zinc and sulphuric acid [5] gave only 1% of the supposed 5-phthalimidothiophen-2-thiol (m. p. 135°). The alkali-soluble product from reduction [6] of the sulphonyl chloride by lithium aluminium hydride

* Part IV, *J.*, 1955, 1071.
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Montmollin and Montmollin, *Helv. Chim. Acta*, 1923, **6**, 94.
[2] Cymerman-Craig and Loder, *J.*, 1954, 237.
[3] Rinkes, *Rec. Trav. chim.*, 1932, **51**, 1134.
[4] Baldwin and Robinson, *J.*, 1932, 1445.
[5] Zinke and Jorg, *Ber.*, 1909, **42**, 3362.
[6] Marvel and Caesar, *J. Amer. Chem. Soc.*, 1950, **72**, 1033.

decomposed on reaction with methyl iodide, and treatment of the sulphonyl chloride with hydriodic acid in acetic acid [7] proved abortive, none of the disulphide being isolated.

An alternative approach was evolved from thiophen-2-sulphonyl chloride, prepared by an improved direct method instead of the customary preparation [8,9] *via* sodium thiophen-2-sulphonate. Nitration by a modification of Burton and Davy's method [9] gave the mixed 4- and 5-nitrothiophen-2-sulphonyl chlorides, containing a somewhat higher proportion of the 5-nitro-compound which was obtained pure for the first time. Reduction of this afforded *N*-(5-sulphonamido-2-thienyl)phthalamic acid, identical with the compound obtained by successive treatment of 5-phthalimidothiophen-2-sulphonyl chloride with ammonia and sodium hydrogen carbonate. This synthesis confirms the 2 : 5-orientation of the compounds derived from 2-phthalimidothiophen in this and an earlier paper,[10] and affords rigid proof of the configuration of 5-nitrothiophen-2-sulphonyl chloride, previously shown [8] (in admixture with the 4-nitro-compound) only to give both 2- and 3-nitrothiophen on hydrolysis and desulphonation.

While 5-phthalimidothiophen-2-sulphonyl chloride and aniline gave 5-phthalimidothiophen-2-sulphonanilide, the more strongly basic 2-aminopyridine caused simultaneous ring-opening, affording 2-(5-*o*-carboxybenzamidothiophen-2′-sulphonamido)pyridine.

Reaction of 2-aminothiophen with succinic anhydride gave *N*-2-thienylsuccinamic acid, cyclised to 2-succinimidothiophen and thence converted, *via* 5-succinimidothiophen-2-sulphonyl chloride, into the sulphonamide. Ring-opening gave *N*-(5-sulphonamido-2-thienyl)succinamic acid, also obtained by reduction of 5-nitrothiophen-2-sulphonamide in presence of succinic anhydride. The identity of the two compounds affords proof of the 2 : 5-orientation of the succinimido-compounds of this series. Those sulphonamides soluble in sodium hydrogen carbonate are being examined for antibacterial activity.

Experimental

Methyl 5-Nitro-2-thienyl Sulphide.—A mixture of nitric acid (7 c.c., *d* 1·51, 0·17 mole) and acetic anhydride (20 c.c.) was added dropwise with stirring to methyl 2-thienyl sulphide (17·5 g., 0·14 mole) in acetic anhydride (25 c.c.) at $< -10°$. The mixture was stirred for a further 0·5 hr. at $-10°$, poured on ice, and extracted with ether. Distillation of the washed (sodium carbonate solution) and dried (Na_2SO_4) extracts gave *methyl 5-nitro-2-thienyl sulphide* (9 g., 40%), b. p. 106—112°/0·01 mm., yellowish plates (from hexane), m. p. 81—82° (Found: C, 34·2; H, 2·8. $C_5H_5O_2NS_2$ requires C, 34·25; H, 2·9%).

Methyl 5-Nitro-2-thienyl Sulphone.—Methyl 5-nitro-2-thienyl sulphide (2 g., 0·011 mole), 30% hydrogen peroxide (5·4 c.c., 0·05 mole), and acetic acid (20 c.c.) were heated at 100° for 45 min., poured on ice, neutralised with 2N-sodium hydroxide, and extracted with ether. Working-up gave the *sulphone* (1·2 g., 50%) as fawn needles (from aqueous alcohol), m. p. 93—94° (Found: C, 29·0; H, 2·6. $C_5H_5O_4NS_2$ requires C, 29·0; H, 2·45%).

Methyl 5-Phthalimido-2-thienyl Sulphone.—A solution of methyl 5-nitro-2-thienyl sulphone (7·5 g., 0·036 mole) and phthalic anhydride (5·4 g., 0·036 mole) in acetic acid (50 c.c.) was treated with water (10 c.c.) and reduced iron powder (10 g., 0·18 mole) for 2 hr. at 50—60°. Stirring was continued for a further 2·5 hr., and the mixture poured into ice-water (300 c.c.) and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution and on removal of solvent gave *methyl 5-phthalimido-2-thienyl sulphone* (8·2 g., 72%), crystallising from chloroform–light petroleum (b. p. 60—90°) as plates, m. p. 220° (Found: C, 50·65; H, 3·05; O, 20·4. $C_{13}H_9O_4NS_2$ requires C, 50·8; H, 2·95; O, 20·8%).

N-(5-Methylsulphonyl-2-thienyl)phthalamic Acid.—Methyl 5-phthalimido-2-thienyl sulphone (2 g.) and saturated sodium hydrogen carbonate solution (20 c.c.) were kept at 100° for 5 min., then filtered and acidified at 0° with 2N-hydrochloric acid, affording the *phthalamic acid* (1·9 g., 90%), crystallising from acetone–light petroleum (b. p. 60—90°) as prisms, m. p. 220° (Found: C, 48·0; H, 3·5. $C_{13}H_{11}O_5NS_2$ requires C, 48·0; H, 3·4%).

5-o-Carboxybenzamidothiophen-2-sulphinic Acid.—(*a*) 5-Phthalimidothiophen-2-sulphonyl

[7] Bauer and Cymerman, *J.*, 1949, 3434.
[8] Steinkopf and Höpner, *Annalen*, 1933, **501**, 174.
[9] Burton and Davy, *J.*, 1948, 525.
[10] Cymerman-Craig and Willis, *J.*, 1955, 1071.

chloride (3·7 g., 0·011 mole) was added slowly to a stirred solution of sodium sulphite heptahydrate (5·4 g., 0·022 mole) in water (30 c.c.) at 70°, the pH being kept at 8 by addition of sodium hydrogen carbonate. Stirring at 70° was continued for a further 2 hr., and the filtered solution acidified at 0° with 2N-sulphuric acid. The white precipitate was washed with ice-water and quickly dried on porous tile over phosphoric oxide, giving the *sulphinic acid* (3·1 g., 94%), m. p. 138° (Found : C, 44·95; H, 3·2. $C_{12}H_9O_5NS_2,0{\cdot}5H_2O$ requires C, 45·0; H, 3·15%).

(*b*) 5-Phthalimidothiophen-2-sulphonyl chloride (1·64 g., 0·005 mole), zinc dust (1 g., 0·015 mole), water (4 drops), and 1 : 2-dimethoxyethane (20 c.c.) were refluxed for 2 hr. The cooled solution was filtered, the solid boiled with a solution of sodium carbonate (1 g.) in water (5 c.c.), the whole filtered, and the filtrate acidified at 0° as in (*a*), affording the sulphinic acid (0·65 g., 42%), m. p. and mixed m. p. 138°. Extraction of the residual zinc salts with chloroform gave 2-phthalimidothiophen (0·4 g., 35%), m. p. and mixed m. p. 198°.

(*c*) Attempted recrystallisation of the sulphinic acid from non-hydroxylic solvents, or drying *in vacuo*, gave *N*-2-thienylphthalamic acid, m. p. and mixed m. p. 185° (Found : C, 58·2; H, 3·75. Calc. for $C_{12}H_9O_3NS$: C, 58·3; H, 3·7%).

(*d*) On attempted recrystallisation of the sulphinic acid from hydroxylic solvents, or on storage of it in acid solution, 2-phthalimidothiophen was formed (m. p. and mixed m. p. 198°) (Found : C, 62·9; H, 3·15. Calc. for $C_{12}H_7O_2NS$: C, 62·8; H, 3·1%).

Methyl N-2-Thienylphthalamate.—The preceding sulphinic acid (1·6 g., 0·005 mole) was dissolved in cold sodium hydrogen carbonate solution and the solution brought to pH 7·5 with dilute nitric acid. Addition of silver nitrate solution gave a white silver salt which was filtered off and refluxed with aqueous methanol (3 : 7) (30 c.c.) and methyl iodide (10 mols.) for 8 hr. Removal of solvent *in vacuo* and addition of water to the residue gave *methyl N-2-thienylphthalamate* (0·7 g., 56%) as needles [from chloroform–light petroleum (b. p. 60—90°)], m. p. 154° (Found : O, 18·2; N, 4·75; S, 12·5. $C_{13}H_{11}O_3NS$ requires O, 18·3; N, 5·25; S, 12·25%).

N-2-Thienylphthalamic Acid.—A benzene solution of 2-aminothiophen, prepared from 2-thienylammonium chlorostannate (5·6 g., 0·01 mole) by the method of Cymerman-Craig and Willis,[10] was shaken with phthalic anhydride (3 g., 0·02 mole) in acetone (50 c.c.) in an inert atmosphere for 1 hr. Removal of solvent *in vacuo*, extraction of the residue with cold saturated sodium hydrogen carbonate (3 × 30 c.c.), and acidification of the extract with 10N-hydrochloric acid gave the phthalamic acid (2·1 g., 41%), m. p. 185°, identical with the material described by Cymerman-Craig and Willis.[10]

2-Phthalimidothiophen.—2-Thienylammonium chlorostannate (10·6 g., 0·02 mole) was added during 15 min. to a stirred solution of sodium acetate (3·28 g., 0·04 mole), phthalic anhydride (5·92 g., 0·04 mole), and acetic acid (100 c.c.) at 60°, and the mixture heated for a further 2 hr., then poured on ice (500 g.) and extracted with chloroform. The extracts afforded yellow needles of 2-phthalimidothiophen (3·8 g., 42%), m. p. 198°, undepressed on admixture with the material of Cymerman-Craig and Willis.[10]

N-(5-Sulphonamido-2-thienyl)phthalamic Acid.—(*a*) 5-Phthalimidothiophen-2-sulphonamide was gently boiled with sodium hydrogen carbonate solution for 5 min., then filtered, and the filtrate acidified at 0° with 2N-hydrochloric acid, giving the *phthalamic acid* as plates, m. p. 261° (Found : C, 44·05; H, 3·45; S, 19·1; O, 24·6. $C_{12}H_{10}O_5N_2S_2$ requires C, 44·15; H, 3·1; S, 19·6; O, 24·5%).

(*b*) When this acid was heated at 200° for 30 min. at 0·01 mm., it re-cyclised to 5-phthalimidothiophen-2-sulphonamide, m. p. 261°, in 80% yield (Found : C, 46·7; H, 2·75. Calc. for $C_{12}H_8O_4N_2S_2$: C, 46·75; H, 2·6%).

5-Phthalimidothiophen-2-sulphonanilide.—A solution of 5-phthalimidothiophen-2-sulphonyl chloride (0·33 g., 0·001 mole) in acetone (10 c.c.) was treated with aniline (0·19 g., 0·002 mole) and set aside for 48 hr. Addition of ether and extraction of the resulting precipitate with benzene gave the *sulphonanilide* (0·21 g., 62%), crystallising from benzene–light petroleum (b. p. 60—90°) as yellow plates, m. p. 226° (Found : C, 56·2; H, 3·3; S, 16·6. $C_{18}H_{12}O_4N_2S_2$ requires C, 56·25; H, 3·15; S, 16·65%).

2-(5′-o-Carboxybenzamidothiophen-2′-sulphonamido)pyridine.—A solution of 5-phthalimidothiophen-2-sulphonyl chloride (0·33 g., 1 mol.) and 2-aminopyridine (0·2 g., 2 mols.) in acetone (10 c.c.) was kept for 48 hr. and worked up by addition of ether and extraction of the precipitate into benzene, affording the *phthalamic acid* as colourless needles (0·1 g., 24%), m. p. 231° (Found : C, 50·4; H, 3·45. $C_{17}H_{13}O_5N_3S_2$ requires C, 50·5; H, 3·25%).

Thiophen-2-sulphonyl Chloride.—Thiophen (75 g., 0·9 mole) was added during 1 hr. to stirred chlorosulphonic acid (300 g., 1·7 moles) at −15°, at such a rate that the temperature did not rise above −5°. After addition of an equal volume of chloroform, the mixture was

poured on ice, and the chloroform layer separated and washed with ice-water. Distillation gave thiophen-2-sulphonyl chloride, b. p. 94—98°/1·5 mm., as a colourless oil (117 g., 72%). Treatment of a sample with ammonia in chloroform gave thiophen-2-sulphonamide, m. p. and mixed m. p. 142°, in quantitative yield. Burton and Davy [9] report a 50% yield of this sulphonyl chloride by Steinkopf and Hopner's method.[8]

5-Nitrothiophen-2-sulphonyl Chloride.—Thiophen-2-sulphonyl chloride (40 g., 0·23 mole) was added during 1 hr. to well-stirred fuming nitric acid (250 g., 165 c.c., 4 moles, *d* 1·51) at 0—5°. After a further 2 hours' stirring at 25—30°, the mixture was cooled, diluted with an equal volume of chloroform and poured on ice (500 g.). Distillation of the dried ($CaCl_2$) chloroform extracts gave 3 fractions: (i) b. p. 96—100°/0·001 mm. (4·7 g.), n_D^{22} 1·6020, (ii) b. p. 100—103°/0·001 mm. (7·3 g.), n_D^{22} 1·6020, (iii) b. p. 103—108°/0·001 mm. (26 g.), n_D^{22} 1·6033. Fractions (i) and (ii) were pure *5-nitrothiophen-2-sulphonyl chloride* (Found: C, 21·1; H, 0·95. $C_4H_2O_4NS_2Cl$ requires C, 21·1; H, 0·9%) and gave a sulphonamide, m. p. 138°. Fraction (iii) was a mixture of 5- and 4-nitrothiophen-2-sulphonyl chlorides, and gave a sulphonamide, m. p. 155°, unchanged on recrystallisation. Burton and Davy [9] report m. p. 156—157° for the mixed sulphonamide. The total yield of mixed sulphonyl chlorides was 38 g. (76%).

5-Nitrothiophen-2-sulphonamide.—The following method was found preferable to that described by Burton and Davy: Dry ammonia was passed into a solution of 5-nitrothiophen-2-sulphonyl chloride in chloroform for 5 min., the chloroform was washed with water and evaporated *in vacuo*, and the residue crystallised from water as fawn plates, m. p. 138° (Found: C, 23·05; H, 2·15. Calc. for $C_4H_4O_4N_2S_2$: C, 23·1; H, 1·95%). Burton and Davy [9] give m. p. 136°.

N-(5-Sulphonamido-2-thienyl)phthalamic Acid from 5-Nitrothiophen-2-sulphonamide.—Preparation from 5-nitrothiophen-2-sulphonamide (1 g., 0·005 mole), phthalic anhydride (0·71 g., 0·005 mole), acetic acid (10 c.c.), and reduced iron powder (1·25 g., 0·02 mole) by the method described for methyl 5-phthalimido-2-thienyl sulphone, and treatment of the product with sodium hydrogen carbonate solution gave, on acidification of the filtrate, *N*-(5-sulphonamido-2-thienyl)phthalamic acid (0·49 g., 31%), crystallising from acetone–light petroleum (b. p. 60—90°) as plates, m. p. 261° (Found: C, 44·15; H, 3·4. Calc. for $C_{12}H_{10}O_5N_2S_2$: C, 44·15; H, 3·1%). A mixed m. p. with the product from 5-phthalimidothiophen-2-sulphonamide was undepressed.

N-2-Thienylsuccinamic Acid.—A benzene solution of 2-aminothiophen, prepared from 2-thienylammonium chlorostannate (5·6 g., 0·01 mole), was added to succinic anhydride (2·1 g., 0·02 mole) in benzene (50 c.c.) in an inert atmosphere. The mixture was shaken for 4 hr., and the solid filtered off and crystallised from acetone–light petroleum (b. p. 60—90°), giving plates, m. p. 167·5°, of the *acid* (2·5 g., 61%) (Found: C, 47·9; H, 4·7; S, 15·85. $C_8H_9O_3NS$ requires C, 48·2; H, 4·6; S, 16·1%).

2-Succinimidothiophen.—After the preceding acid (2 g.) had been heated at 175° for 2 min., the residue was extracted with benzene and purified by passage through a column of alumina, *2-succinimidothiophen* (1·1 g., 61%) being obtained as needles, m. p. 150—150·5° (decomp.) (Found: C, 53·4; H, 4·15; O, 17·3. $C_8H_7O_2NS$ requires C, 53·05; H, 3·9; O, 17·6%).

5-Succinimidothiophen-2-sulphonyl Chloride.—Reaction of 2-succinimidothiophen (5·7 g., 0·03 mole) and chlorosulphonic acid (18·3 g., 1·05 mole) at −5° by the method used for the preparation of the phthalimido-analogue by Cymerman-Craig and Willis,[10] gave *5-succinimidothiophen-2-sulphonyl chloride* (2·65 g., 30%) as needles (from chloroform), m. p. 138—140° (Found: C, 34·55; H, 2·6; N, 4·8; S, 23·0. $C_8H_6O_4NS_2Cl$ requires C, 34·35; H, 2·2; N, 5·0; S, 22·95%).

5-Succinimidothiophen-2-sulphonamide.—Treatment of the foregoing sulphonyl chloride (0·7 g.) in chloroform (30 c.c.) with dry ammonia, followed by purification of the product by dissolution in cold N-sodium hydroxide and precipitation at 0° with 2N-hydrochloric acid, gave the *sulphonamide* (0·6 g., 90%) as needles, m. p. 218° (Found: C, 36·0; H, 3·6. $C_8H_8O_4N_2S_2$ requires C, 36·0; H, 3·1%).

N-(5-Sulphonamido-2-thienyl)succinamic Acid.—(*a*) A solution of 5-succinimidothiophen-2-sulphonamide (0·32 g.) in N-sodium hydroxide (4·5 c.c.) was set aside at room temperature for 24 hr. The solution was acidified with 2N-hydrochloric acid, giving the *acid* (0·24 g., 69%) as prisms, m. p. 216—218° (decomp.) (Found: C, 34·25; H, 4·0; O, 28·5; N, 9·7; S, 23·25. $C_8H_{10}O_5N_2S_2$ requires C, 34·5; H, 3·65; O, 28·7; N, 10·0; S, 23·05%).

(*b*) Preparation from 5-nitrothiophen-2-sulphonamide (1 g.) and succinic anhydride (0·5 g., 1 mol.) by reduction with iron powder in acetic acid, as described above for the analogous phthalamic acid, gave the acid as plates, m. p. 216° (decomp.) (0·5 g., 30%) (Found: C, 34·85;

H, 3·8%). When the acid (0·4 g.) was heated for 5 min. at 200°/1 mm., it cyclised to give 5-succinimidothiophen-2-sulphonamide (0·3 g., 60%), crystallising from acetone–light petroleum (b. p. 60—90°) as needles, m. p. 218°, undepressed on admixture with the substance obtained from 5-succinimidothiophen-2-sulphonyl chloride.

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795. *Purines, Pyrimidines, and Glyoxalines. Part IV.* Cyanouracils from Amines and Amino-acids.†*

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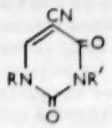
Cyanoethoxyacrylamide derivatives, CN·C(:CH·OEt)·CO·NR′·CO_2Et, react with amines and amino-acids, forming 5-cyanouracils. Intermediate aminoacrylamides CN·C(:CH·NHR)·CO·NR′·CO_2Et, isolated in a number of cases, cyclised to the cyanouracils when warmed or in alkali.

DERIVATIVES of uracil, substituted at $C_{(5)}$ with such groups as bromo, chloro, nitro, and hydroxy, inhibit the growth of a number of organisms.[1] 5-Bromouracil is incorporated into nucleic acids,[2] and the growth-inhibition of micro-organisms which it causes is reversed by thymine and thymidine.[3,4] 5-Cyanouracils are closely related to thymine, and their potential action as metabolite antagonists is being studied.

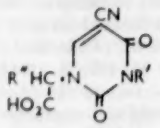
5-Cyanouracil, its 1-methyl derivative, and the anilinoacrylamide (II; R = Ph, R′ = H) have been prepared (cf. Part I) by treating ammonia, methylamine, and aniline respectively with the ethoxyacrylamide (I; R′ = H; referred to below as "the ethoxyacrylamide"). When heated near its melting point the anilinoacrylamide cyclised to 5-cyano-1-phenyluracil. The structure of 5-cyanouracil was shown by hydrolysis and decarboxylation to uracil. This is probably the most convenient method available for the synthesis of *N*-substituted uracils with an unambiguous orientation of substituents. The

(I) CN·C(:CH·OEt)·CO·NR′·CO_2Et

(II) CN·C(:CH·NHR)·CO·NR′·CO_2Et



(III)



(IV)

reaction has been applied to glycosylamines (cf. Part II). Conditions have now been found for the preparation of 5-cyanouracils and 5-cyano-3-methyluracils from amines, amino-acids, and hydrazines. Intermediate aminoacrylamides have been isolated in a number of cases; these compounds cyclise to uracil derivatives in alkali, and this procedure facilitates the preparation of uracils with heat-sensitive substituents.

With ethylamine, aromatic primary amines, or benzamide the ethoxyacrylamide gave aminoacrylamides (II; R = Et, aryl, or Bz, R′ = H), while with secondary amines it gave acrylamides CN·C(:CH·NR_2)·CO·NH·CO_2Et. In the presence of an excess of aliphatic amine 1-alkyl-5-cyanouracils were formed in nearly quantitative yields and aminoacrylamides could not be isolated. An excess of aromatic amine did not promote cyclisation of arylaminoacrylamides; these were, however, converted into pyrimidines by alkali. The *N*-methyl derivative of the ethoxyacrylamide (I; R′ = Me; referred to below as "the

* Parts I—III, *J.*, 1955, 1834; 1956, 1877, 3847.
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] See Roblin, *Ann. Rev. Biochem.*, 1954, **23**, 506, 515.
[2] Weygand, Wacker, and Dellweg, *Z. Naturforsch.*, 1952, **7**b, 19.
[3] Weygand, Wacker, and Grisebach, *ibid.*, 1951, **6**b, 177.
[4] Hitchings, Elion, Falco, Russell, Sherwood, and VanderWerff, *J. Biol. Chem.*, 1950, **183**, 1.

ethoxy-*N*-methylacrylamide") was more reactive, forming 5-cyano-3-methyl-1-phenyluracil when treated with ethanolic aniline. α-Amino-acids in alkaline solution reacted with the ethoxyacrylamides, forming uracil-1-acetic acids (IV; R′ = H or Me).

Cyanouracils are useful derivatives of amines and amino-acids. These compounds may be separated, identified, and estimated by paper chromatography, ion-exchange, and ultraviolet spectrophotometry. The absorption spectra resemble those of uracil derivatives, but the cyano-group causes a slight bathochromic shift.

A cyanouracil derivative of glycylglycine (III; R = CH_2·CO·NH·CH_2·CO_2H, R′ = H) has now been prepared in nearly quantitative yield and without cleavage of the peptide bond. Acid hydrolysis of this bond took place without destruction of the pyrimidine ring, but the nitrile was hydrolysed. Ethoxyacrylamides in which the cyano-group is replaced by acid-stable structures are now being examined as reagents for the *N*-terminal residues of proteins.

Pyrimidines prepared by these methods are being tested as inhibitors of tumour-growth in the Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research.

Experimental

Unless otherwise indicated, compounds were dried over phosphoric oxide at 55°/0·1 mm. before analysis; spectra were measured in M/100-aqueous sodium borate (pH 9·4), and R_F values were determined on Whatman No. 1 paper in a solvent containing propan-2-ol (95%; 68 ml.), hydrochloric acid (10N; 20 ml.), water (12 ml.).

N-Cyanoacetylurethane.—Cyanoacetic acid (8·5 g.), urethane (8·9 g.), and phosphoryl chloride (7·6 g.) were heated at 70° (bath). Evolution of hydrogen chloride started after 15 min. and continued for a further 15 min.; then crystallisation took place. The suspension was chilled and diluted with water (35 ml.) before recovery of the *N*-cyanoacetylurethane (12·5 g.), m. p. 166°. The compound crystallised from ethanol as colourless plates (11·7 g., 75%), m. p. and mixed m. p. 168° (cf. Conrad and Schulze [5]).

α-Cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide, m. p. 122°, was prepared from *N*-cyanoacetylurethane (cf. Part I). The compound, recrystallised from ethyl acetate, was obtained in yields of 55—75%.

5-Cyanouracils from Primary Aliphatic Amines.—A suspension of the ethoxyacrylamide (2·0 g.) in a solution of ethylamine (0·85 g.) in water (10 ml.) was warmed for 10 min. The resultant solution was cooled and acidified with hydrochloric acid (10N; 2 ml.); *5-cyano-1-ethyluracil* (1·49 g., 96%), m. p. 208—209°, was precipitated immediately. The compound crystallised from ethanol as colourless prisms, m. p. 209° (R_F = 0·63; ε 8·8 × 10^3, $\lambda_{max.}$ 279 mμ) (Found: C, 51·2; H, 4·3; N, 25·3. $C_7H_7O_2N_3$ requires C, 50·9; H, 4·3; N, 25·45%). Other *5-cyanouracils* prepared in this way from primary amines are shown in Table 1.

Table 1. *1-Alkyl-5-cyanouracils* (III; R′ = H).

R	M. p.	Yield (%)	R_F [a]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
Pr[n]	165° [b]	95	0·75	53·7	4·9	23·4	$C_8H_9O_2N_3$	53·6	5·1	23·45
Pr[i]	274	72 [c]	0·68	53·5	4·8	23·5				
Bu[n]	190 [d]	98	0·76	55·85	5·6	21·7	$C_9H_{11}O_2N_3$	55·95	5·7	21·75
Bu[s]	265	97	0·79	55·7	5·7	21·8				
Bu[i]	221	73 [c]	0·80	55·9	5·6	21·7				
n-Pentyl	176	50 [c]	0·84	57·85	6·2	20·4	$C_{10}H_{13}O_2N_3$	58·0	6·3	20·3
i-Pentyl	215	58 [c]	0·86	57·7	6·1	20·5				
Ph·CH_2	234	65 [c]	0·78	63·7	4·1	18·6	$C_{13}H_9O_2N_3$	63·4	4·0	18·5
*cyclo*Hexyl	324	97	—	60·0	5·85	19·2	$C_{11}H_{13}O_2N_3$	60·3	6·0	19·15

[a] The previously described compounds with R = H and R = Me (cf. Part I) had R_F = 0·32 and 0·43; the latter had ε 8·3 × 10^3, $\lambda_{max.}$ 278 mμ. [b] ε 8·9 × 10^3, $\lambda_{max.}$ 280 mμ. [c] Yield of thrice recrystallised analytical material. [d] ε 9·6 × 10^3, $\lambda_{max.}$ 280 mμ.

Aminoacrylamides from Amines and the Ethoxyacrylamide.—(a) *Reaction with ethylamine.* The ethoxyacrylamide (1·25 g.) in ethanol (20 ml.) was mixed at 0—5° with a solution of ethylamine (0·26 g.) in aqueous ethanol (95%; 4 ml.). The solution was cooled to −50°, *α-cyano-N-ethoxycarbonyl-β-ethylaminoacrylamide* (0·90 g., 72%) crystallising as colourless needles, m. p.

[5] Conrad and Schulze, *Ber.*, 1909, **42**, 734.

144° (Found : C, 51·3; H, 6·4; N, 19·9. $C_9H_{13}O_3N_3$ requires C, 51·2; H, 6·2; N, 19·9%). The compound could be recrystallised from warm acetone without decomposition, but when its solution in ethanol was boiled 5-cyano-1-ethyluracil was formed.

(b) *Reaction with aromatic and heterocyclic amines.* Solutions of the ethoxyacrylamide (5·0 g.) in ethanol (50 ml.), and sulphanilamide (4·1 g.) in ethanol (50 ml.), were mixed and warmed until no more solid separated. The resultant suspension was stored at 5° overnight, and *α-cyano-N-ethoxycarbonyl-β-p-sulphamoylanilinoacrylamide* (6·2 g., 78%) was collected (m. p. 213—214°). The compound crystallised from ethanol as colourless needles, m. p. 214° (Found : C, 46·2; H, 4·4; N, 16·55. $C_{13}H_{14}O_5N_4S$ requires C, 46·15; H, 4·2; N, 16·6%). Other *aminoacrylamides*, prepared similarly, are shown in Table 2.

(c) *Reaction with secondary amines.* The ethoxyacrylamide (0·5 g.) in ethanol (15 ml.) was warmed for 15 min. with ethanolic dimethylamine (33% w/v; 0·33 ml.). *α-Cyano-β-dimethylamino-N-ethoxycarbonylacrylamide* (0·10 g., 20%), m. p. 142° crystallised from the cooled solution, and a further portion (0·13 g., 27%), m. p. 142°, was recovered after concentration of the solution. Crystallisation from acetone did not raise the m. p. (ε 24·2 × 10^3, $\lambda_{max.}$ 296 mμ) (Found : C, 51·3; H, 6·2; N, 19·9. $C_9H_{13}O_3N_3$ requires C, 51·2; H, 6·2; N, 19·9%).

The ethoxyacrylamide (1·0 g.) and diethylamine (0·35 g.) similarly gave *α-cyano-β-diethylamino-N-ethoxycarbonylacrylamide* (0·73 g., 65%), which, crystallised from acetone at −50°, had m. p. 90° (Found : C, 55·4; H, 7·2; N, 17·35. $C_{11}H_{17}O_3N_3$ requires C, 55·2; H, 7·2; N, 17·55%).

(d) *Reaction with benzamide.* The acrylamide (1·0 g.) and benzamide (0·57 g.) were heated for 30 min. at 160° (bath). *β-Benzamido-α-cyano-N-ethoxycarbonylacrylamide*, which was obtained on cooling, crystallised from acetone as needles (0·66 g., 59%), m. p. 158° (Found : C, 58·5; H, 4·8; N, 14·85. $C_{14}H_{13}O_4N_3$ requires C, 58·5; H, 4·6; N, 14·6%).

TABLE 2. *Substituted β-amino-α-cyano-N-ethoxycarbonylacrylamides* (II).

			Found (%)				Required (%)		
R	M. p.	Yield (%)	C	H	N	Formula	C	H	N
p-C_6H_4·NO_2	198°	92	51·3	3·7	18·65	$C_{13}H_{12}O_4N_4$	51·3	4·0	18·4
p-C_6H_4·CO_2H ...	220	92	55·2	4·3	13·65	$C_{14}H_{13}O_5N_3$	55·45	4·3	13·9
2-Naphthyl	156	82	66·0	5·1	13·3	$C_{17}H_{15}O_3N_3$	66·0	4·9	13·6
2-Pyridyl	256	81	55·0	4·9	21·9	$C_{12}H_{12}O_3N_4$	55·4	4·65	21·5
3-Pyridyl	160°	81	55·4	4·8	21·65				

° Decomposes and immediately resolidifies above the m. p.

Cyclisation of Aminoacrylamides to Substituted Uracils.—A suspension of β-anilino-α-cyano-*N*-ethoxycarbonylacrylamide (cf. Part I) (0·2 g.) in aqueous sodium hydroxide (N; 5 ml.) was warmed at 80° to produce a clear solution, which was cooled and acidified with hydrochloric acid. 5-Cyano-1-phenyluracil (0·12 g.) was precipitated and crystallised from ethanol as colourless plates, m. p. and mixed m. p. 290° (cf. Part I).

When α-cyano-*N*-ethoxycarbonyl-β-phenylhydrazinoacrylamide (cf. Part I) (0·25 g.) was treated with alkali, as in the case of the anilinoacrylamide, 1-anilino-5-cyanouracil (0·15 g.), m. p. and mixed m. p. 334° (cf. Part I), was obtained.

α-Cyano-*N*-ethoxycarbonyl-β-*p*-nitroanilinoacrylamide (0·50 g.) was boiled with aqueous sodium hydroxide (2N; 10 ml.) for 30 min. The red solution was cooled and acidified with hydrochloric acid (10N; 2·1 ml.), *1-p-nitrophenyluracil-5-carboxyamide* (0·27 g., 60%) being precipitated (m. p. 327—328°). When recrystallised from water the product had m. p. 328° (Found, in material dried for 3 hr. at 100°/0·1 mm. : C, 47·8; H, 3·0; N, 20·1. $C_{11}H_8O_5N_4$ requires C, 47·8; H, 2·9; N, 20·3%).

Reaction of the Ethoxyacrylamide with Hydrazine.—Hydrazine hydrate (60% w/v; 0·4 ml.) was added to the ethoxyacrylamide (1·0 g.) in hot ethanol (10 ml.), and the solution was boiled for 5 min. A mixture of compounds (0·65 g.) crystallised from the cooled solution, and was separated into two approximately equal fractions by crystallisation from ethanol. The less soluble compound, which was identified as *1-amino-5-cyanouracil*, crystallised from ethanol as pale yellow plates, m. p. 288° (Found : C, 39·5; H, 2·7; N, 37·0. $C_5H_4O_2N_4$ requires C, 39·5; H, 2·65; N, 36·8%). The more soluble *hydrazinium salt* crystallised from ethanol as cream needles which darkened on exposure to air. The salt had m. p. 142°, but resolidified above the m. p. and then did not melt below 360° (Found : C, 32·9; H, 5·0; N, 45·6. $C_5H_8O_2N_6$ requires C, 32·6; H, 4·4; N, 45·6%).

5-Cyanouracils from the Ethoxyacrylamide and α-Amino-acids.—The ethoxyacrylamide (5·0 g.)

was shaken with a solution of glycine (1·8 g.) in aqueous sodium hydroxide (2N; 12 ml.). When most of the ethoxyacrylamide had dissolved (15 min.) a second portion of sodium hydroxide (10N; 2·4 ml.) was added, and the resultant solution was warmed for 5 min. Addition of hydrochloric acid to the cooled mixture precipitated *5-cyanouracil-1-acetic acid* (3·9 g., 85%) which crystallised from water as needles, m. p. 233° (decomp.), R_F 0·44 (Found: C, 43·35; H, 2·6; N, 21·7. $C_7H_5O_4N_3$ requires C, 43·1; H, 2·6; N, 21·5%).

When an alkaline solution, obtained as above from the same amounts of reactants but without the second equivalent of alkali, was diluted with ethanol (20 ml.) and ether (30 ml.) *sodium 5-cyanouracil-1-acetate monohydrate* (5·2 g., 93%) crystallised, having m. p. >300° (Found: C, 35·7; H, 2·5. $C_7H_4O_4N_3Na,H_2O$ requires C, 35·75; H, 2·5%).

Other *5-cyanouracil-1-acetic acids* prepared by the former procedure are described in Table 3. Compounds which did not crystallise from the acidified reaction mixture were isolated by

TABLE 3. *5-Cyanouracil-1-acetic acids* (IV; R′ = H).

No.	R	Generating acid	R_F	Yield (%)	M. p.[a]
1	Me[a,b]	DL-Alanine	0·58	94	202°
2	Pr[n]	DL-Norvaline	0·80	93	176
3	Pr[i]	DL-Valine	0·77	56	254
4	Bu[n]	DL-Norleucine	0·80	99	196
5	Bu[s]	DL-Isoleucine	0·81	92	198
6	Bu[i][d,e]	L-Leucine	0·80	73	206
7	*n*-Pentyl	DL-α-Amino-*n*-octanoic acid	0·88	90	137
8	$HO{\cdot}CH_2{\cdot}CH_2$[e]	DL-Serine	0·44	91	168
9	$MeS{\cdot}[CH_2]_2{\cdot}CH_2$[e]	DL-Methionine	0·69	51	161
10	$HO_2C{\cdot}CH_2$[f,g]	DL-Aspartic acid	0·53	52	218
11	$H_2N{\cdot}CO{\cdot}CH_2$	DL-Asparagine	0·23	81	189
12	,,	L- ,,	—	92	198
13	$HO_2C{\cdot}CH_2{\cdot}CH_2$[f,g]	DL-Glutamic acid	0·50	42	193
14	,,	L- ,,	—	—	191
15	$Ph{\cdot}CH_2$[d,h]	DL-Phenylalanine	0·80	64	186
16	p-$HO{\cdot}C_6H_4{\cdot}CH_2$[i]	L-Tyrosine	0·74	96	234

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
1	45·9	3·5	20·1	$C_6H_7O_4N_3$	45·9	3·4	20·1
2	50·8	4·65	17·45	$C_{10}H_{11}O_4N_3$	50·6	4·7	17·7
3	50·25	4·45	17·5				
4	52·8	5·1	16·9				
5	52·75	5·0	16·7	$C_{11}H_{13}O_4N_3$	52·6	5·2	16·7
6	52·8	5·25	16·9				
7	55·7	6·0	14·9	$C_{13}H_{17}O_4N_3$	55·9	6·1	15·05
8	41·35	3·4	18·0	$C_6H_7O_5N_3,\frac{1}{2}H_2O$	41·0	3·4	17·95
9	44·4	3·9	15·2	$C_{10}H_{11}O_4N_3S$	44·6	4·1	15·6
10	42·6	3·0	16·7	$C_9H_7O_6N_3$	42·7	2·8	16·6
11	43·05	3·05	22·1	$C_9H_9O_4N_4$	42·9	3·2	22·2
12	42·7	3·0	22·3				
13	44·9	3·75	15·7	$C_{10}H_9O_6N_3$	44·95	3·4	15·7
14	44·7	3·6	15·7				
15	58·9	3·7	14·8	$C_{14}H_{11}O_4N_3$	58·9	3·9	14·7
16	56·1	3·8	13·4	$C_{14}H_{11}O_5N_3$	55·8	3·7	13·95′

[a] Recryst. from ethyl acetate–light petroleum (b. p. 40—60°). [b] Treatment of an ethanolic suspension of the lead salt with hydrogen sulphide afforded the *ethyl ester*, m. p. 112° (Found: C, 50·7; H, 5·0; N, 17·7. $C_{10}H_{11}O_4N_3$ requires C, 50·6; H, 4·7; N, 17·7%). [c] With decomp. [d] The *monohydrate* had m. p. 181°, $[\alpha]_D^{17}$ −50·4° (*c* 1·19 in H_2O) (Found: C, 48·7; H, 5·2; N, 15·6. $C_{11}H_{13}O_4N_3,H_2O$ requires C, 49·1; H, 5·6; N, 15·6%). [e] $[\alpha]_D^{19}$ −48·8° (*c* 0·98 in H_2O). [f] Isolated from the aqueous solution by continuous extraction with ethyl acetate. [g] Purified for analysis by displacement from a Deacidite FF column. [h] Analytical material was isolated directly from the reaction mixture by ion-exchange. [i] Dried for 3 hr. at 78°/1 mm. [j] $[\alpha]_D^{16\cdot6}$ −169° (*c* 2·37 in H_2O). [k] Dried material was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), then from water.

continuous extraction with ethyl acetate or by anion-exchange. Except where indicated, the compounds are racemic mixtures.

Reaction of the Ethoxyacrylamiae with Lysine.—DL-Lysine monohydrochloride (1·87 g.) was dissolved in aqueous sodium hydroxide (1·8N; 11·4 ml.), and sufficient ethoxyacrylamide was added (4·4 g.) to form cyanouracil substituents at both amino-groups. After the addition of

more sodium hydroxide (1·8N; 11·4 ml.) the *product* was isolated in the usual way. This compound crystallised from water as the hemihydrate (2·8 g., 68%), m. p. 218—220° with sintering at 160—170° (Found: C, 48·6; H, 3·8; N, 21·5. $C_{16}H_{14}O_6N_6,\frac{1}{2}H_2O$ requires C, 48·6; H, 3·8; N, 21·3%). Treatment of the lead salt in ethanol with hydrogen sulphide gave the *ethyl ester*, m. p. 263° (Found: C, 52·2; H, 4·5; N, 20·3. $C_{18}H_{18}O_6N_6$ requires C, 52·2; H, 4·4; N, 20·3%).

Reaction of the Ethoxyacrylamide with β-Amino-α-methylpropionic Acid.—The ethoxyacrylamide (5·0 g.) and the DL-amino-acid (2·43 g.) were treated with alkali, and the mixture acidified; *5-cyanouracil-1-(α-methylpropionic acid)* (5·20 g., 99%) was precipitated and collected (m. p. 273—274°). The compound crystallised from water as colourless needles, m. p. 275° (Found: C, 48·2; H, 3·9; N, 19·1. $C_9H_9O_4N_3$ requires C, 48·4; H, 4·1; N, 18·8%).

Purification of 5-Cyanouracil-1-acetic Acids by Anion-exchange.—When solutions of the acids were applied to multiple columns of Deacidite FF (acetate form) following the procedure reported by Anet and Reynolds,[6] acetate was displaced and the pyrimidines were retained by the resin. Hydrochloric acid displaced the pyrimidines, which were isolated analytically pure by evaporation of appropriate fractions of effluent. Thus 5-cyanouracil-1-acetic acid was isolated directly from the reaction mixture, obtained in the usual way, after acidification with acetic acid (Found: C, 43·1; H, 2·7; N, 21·4%). Other examples of compounds purified in this way are included in Table 3. The pyrimidines were located in the effluent from the column by measurement of ultraviolet absorption or optical rotation. In all cases the resin in contact with the pyrimidine showed a light band which facilitated location of the compound.

5-Cyano-3-methyluracils.—α-Cyano-β-ethoxy-*N*-ethoxycarbonyl-*N*-methylacrylamide, b. p. 138°/0·4 mm., was prepared from *N*-cyanoacetyl-*N*-methylurethane (cf. Part II).

The ethoxy-*N*-methylacrylamide (1·0 g.) was added to a solution of ethylamine (0·40 g.) in ethanol (6 ml.). The mixture was heated on a steam-bath until solution was complete and the volume was reduced to 2 ml. On cooling, *5-cyano-1-ethyl-3-methyluracil* (0·67 g., 85%) was precipitated, and crystallised from ethanol as colourless needles, m. p. 133° (Found: C, 53·6; H, 5·3; N, 23·45. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·1; N, 23·45%). Other 5-cyano-3-methyluracils prepared in the same way are described in Table 4.

TABLE 4. *5-Cyano-3-methyluracils* (III; R′ = Me).

				Found (%)			Required (%)		
R	Yield (%)	M. p.	Formula	C	H	N	C	H	N
Me	40	156°	$C_7H_7O_2N_3$	50·9	4·15	25·6	50·9	4·3	25·45
Ph	83	235	$C_{12}H_9O_2N_3$	63·4	4·1	18·3	63·4	4·0	18·5
p-$HO_2C{\cdot}C_6H_4$ [a]	[c]	278	$C_{13}H_9O_4N_3$	57·85	3·5	15·75	57·6	3·3	15·5
$HO_2C{\cdot}CH_2$ [b]	[c]	110	$C_8H_7O_4N_3,H_2O$	42·5	4·1	18·7	42·3	4·0	18·5
2-Pyridyl	64	204	$C_{11}H_8O_2N_4$	58·1	3·6	24·3	57·9	3·5	24·55
3- "	64	167		58·05	3·7	24·45			
H_2N	60	128	$C_6H_6O_2N_4$	43·5	3·7	33·45	43·4	3·6	33·7
Ph·NH	78	210	$C_{12}H_{10}O_2N_4$	59·2	3·95	23·35	59·5	4·2	23·1

[a] Formed from the non-cyclic aminoacrylamide (see below) by the usual treatment with alkali. [b] Sodium hydroxide was added, as with the examples in Table 3. [c] Prepared on a small scale.

Aminoacrylamides from the Ethoxy-N-methylacrylamide.—A mixture of the ethoxy-*N*-methylacrylamide (1·0 g.) and *p*-aminobenzoic acid (0·74 g.) in ethanol (20 ml.) was warmed for 10 min. *β-p-Carboxyanilino-α-cyano-N-ethoxycarbonyl-N-methylacrylamide* (1·1 g., 80%) separated and, recrystallised from acetone, had m. p. 254° (decomp.) (Found: C, 56·9; H, 5·05; N, 13·4. $C_{15}H_{15}O_5N_3$ requires C, 56·8; H, 4·8; N, 13·2%).

With sulphanilamide (2·0 g.) the ethoxy-*N*-methylacrylamide (2·6 g.) gave *β-p-sulphamoylanilino-α-cyano-N-ethoxycarbonyl-N-methylacrylamide* (3·4 g., 84%), m. p. 140° (decomp.) (Found: C, 47·6; H, 4·4; N, 15·75. $C_{14}H_{16}O_5N_4S$ requires C, 47·7; H, 4·6; N, 15·9%)

Hydrolysis of the 5-Cyano-group.—(a) *Alkaline hydrolysis.* 5-Cyanouracil-1-acetic acid (1·95 g.) was heated at 85—95° for 2 hr. with aqueous sodium hydroxide (2·5N; 25 ml.). Addition of hydrochloric acid (10N; 7 ml.) to the cooled solution precipitated a product (1·15 g.), m. p. 267° after softening from 254°. Repeated recrystallisation from ethanol and from water gave *5-carbamoyluracil-1-acetic acid monohydrate* as colourless needles, m. p. 275° (decomp.) (Found: C, 36·6; H, 4·4; N, 17·9. $C_7H_7O_5N_3,H_2O$ requires C, 36·4; H, 3·9; N, 18·2%).

(b) *Acid hydrolysis.* 5-Cyanouracil-1-acetic acid (3·6 g.) was boiled under reflux with

[6] Anet and Reynolds, *Austral. J. Chem.*, 1955, **8**, 267.

hydrochloric acid (6N; 75 ml.) for 8 hr. The solution was concentrated to 15 ml. and *5-carboxyuracil-1-acetic acid* (1·1 g.) crystallised [m. p. 247° (decomp.)]. This material crystallised from water as colourless plates, m. p. 275° (decomp.; softens above 250°) (Found: C, 39·4; H, 3·0; N, 13·35. $C_7H_6O_6N_2$ requires C, 39·3; H, 2·9; N, 13·1%).

When 5-cyano-1-α-carboxyphenethyluracil (50 mg.) was similarly hydrolysed with hydrochloric acid (6N; 2 ml.), the *5-carboxylic acid* crystallised, and when washed with water (5 ml.) had m. p. 222° (decomp.) (Found: C, 55·3; H, 4·0; N, 9·25. $C_{14}H_{12}O_6N_2$ requires C, 55·3; H, 4·0; N, 9·2%).

Identification of the N-Terminal Residue in a Peptide.—Glycylglycine (3·1 g.) was converted into *5-cyanouracil-1-(N-carboxymethylacetamide)* (III; R = $HO_2C{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2$, R′ = H) by treatment with the ethoxyacrylamide (5·0 g.) in a reaction similar to that used for the compounds described in Table 3. The cyanouracil derivative crystallised from water as colourless plates (5·3 g., 90%), m. p. 251—253° (decomp.; darkens above 200°) (Found: C, 42·6; H, 3·3; N, 22·3. $C_9H_8O_5N_4$ requires C, 42·9; H, 3·2; N, 22·2%).

Samples (*ca.* 10 mg.) of the 5-cyanouracils derived from glycylglycine and from glycine were boiled under reflux in hydrochloric acid (6N; 2 ml.) for 8 hr. and then evaporated to dryness. Paper chromatograms were run under the conditions described above. Both hydrolysates showed single spots (R_F 0·75, 0·77) which absorbed ultraviolet light and corresponded to 5-carboxyuracil-1-acetic acid. The hydrolysate of the cyanouracil from glycylglycine also showed a spot (R_F 0·44) which reacted with ninhydrin and corresponded to glycine.

Paper Chromatography of Derivatives formed from Ammonia, Methylamine, and Dimethylamine.—The pyrimidines formed from ammonia and methylamine, and the dimethylaminoacrylamide formed from dimethylamine on treatment with the ethoxyacrylamide, were separated by chromatography on Whatman No. 1 paper in a solvent of water (100 ml.)–propan-2-ol (95%; 5 ml.)–ammonium sulphate (5 g.). The compounds were detected as discrete ultraviolet-absorbing spots (R_F values 0·76, 0·85, and 0·93 respectively).

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796. *The Aporphine Series. Part II.* Application of the Bischler–Napieralski Reaction to 2-Nitrophenyl-N-phenethylacetamides.*†

By D. H. Hey and A. L. Palluel.

A re-examination of Späth and Hromatka's synthesis of *apo*morphine dimethyl ether (I) has shown that the action of phosphoric oxide on 3:4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = $CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2Ph$) gives a mixture of 1-(3:4-dimethoxy-2-nitrobenzyl)-3:4-dihydro*iso*quinoline (II) and the phenethylamide of 6:7-dimethoxyanthranil-3-carboxylic acid (IV; R = $NH{\cdot}CH_2{\cdot}CH_2Ph$). The former was converted into DL-*apo*morphine dimethyl ether (I); the latter was synthesised independently from 3:4-dimethoxy-2-nitrophenylacetic acid and from 3:4-dimethoxy-2-nitromandelic acid. The alternative ketenimine and acetylenic structures previously assigned to the neutral by-products formed when the Bischler–Napieralski reaction is applied to certain 2-nitrophenyl-*N*-phenethylacetamides must be rejected.

The synthesis of *apo*morphine dimethyl ether (I) reported by Späth and Hromatka in 1929 [1] has been the subject of considerable interest. Their method had previously been

* Part I, *J.*, 1954, 2246.

† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Späth and Hromatka, *Ber.*, 1929, **62**, 326.

attempted by Kay and Pictet [2] and by Kondo [3] without success, and a similar failure was reported by Gulland, Haworth, Virden, and Callow [4] at about the time when Späth and Hromatka announced their success. The stage in the synthesis upon which particular interest is centred, namely, the application of the Bischler–Napieralski reaction to 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) to give 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (II), was reinvestigated by Hey and Lobo.[5] Although a variety of experimental conditions and reagents was used in an attempt to effect ring closure to the dihydro*iso*quinoline, no positive evidence for such ring closure was obtained, but the presence of a trace of a basic product in one experiment led to the further reinvestigation reported in this communication.

It is significant that Späth and Hromatka's synthesis of 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (II) from 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) provided the only known example of the ring closure of an *o*-nitrophenyl-*N*-phenethylacetamide into a 3 : 4-dihydro*iso*quinoline in which the nucleus involved in the ring closure is not activated by the presence of a suitable substituent atom or group (see Whaley and Govindachari [6]). Further, it has been noted by all the groups of workers that, whenever 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) is subjected to the experimental conditions required for the Bischler–Napieralski reaction, there is invariably formed a neutral by-product, which is isomeric with the desired 3 : 4-dihydro*iso*quinoline. Similar neutral products have also been reported by Kondo and Ishiwata [7] in the attempted cyclisation of *N*-(3-bromo-4-methoxyphenethyl)-3 : 4-dimethoxy-2-nitrophenylacetamide, and by Callow, Gulland, and Haworth [8] in that of 3 : 4-dimethoxy-2-nitrophenyl-*N*-*p*-methoxyphenethylacetamide and of a similar compound prepared from β-3-amino-4-methoxyphenethylamine (see also Gulland, Haworth, Virden, and Callow [4]). These neutral compounds have always been represented as either (*a*) keten-imines (*e.g.*: III; R = CH:C:N·CH_2·CH_2Ph) or (*b*) acetylenic compounds (*e.g.*: III; R = C:C·NH·CH_2·CH_2Ph), but adequate experimental evidence to establish one or other of these structures has never been obtained.

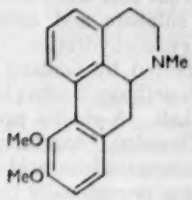
After work had been initiated on a general study of the application of the Bischler–Napieralski reaction to *o*-nitrophenyl-*N*-phenethylacetamides with the double objective of establishing (*a*) the experimental conditions necessary for ring closure to the 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinolines, and (*b*) the identity of the neutral isomeric by-products, it was reported by Govindachari and Nagarajan [9] that, using the conditions of Späth and Hromatka, they had been able to prepare 3 : 4-dihydro-1-2′-nitrobenzyl-*iso*quinoline in about 25% yield from 2-nitrophenyl-*N*-phenethylacetamide. This reaction, which provided only the second example of the ring closure of an *o*-nitrophenyl-*N*-phenethylacetamide involving an unactivated aromatic nucleus, has also been successfully carried out independently by the present authors and has been briefly reported.[10]

It has now been found that when 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) is boiled under reflux in toluene solution in the presence of phosphoric oxide the product consists of a mixture of approximately equal parts of a neutral compound and 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro-*iso*quinoline (II). The isolation of the latter compound was assisted by the solubility of its hydrochloride in chloroform. When the same ring-closure was attempted with phosphorus pentachloride in boiling benzene solution the sole identified product was the neutral compound referred to above, which has now been shown to be the phenethylamide (IV;

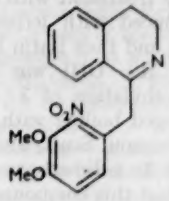
[2] Kay and Pictet, *J.*, 1913, 947.
[3] Kondo, *J. Pharm. Soc. Japan*, 1925, **519**, 429.
[4] Gulland, Haworth, Virden, and Callow, *J.*, 1926, 1666.
[5] Hey and Lobo, *J.*, 1954, 2246.
[6] Whaley and Govindachari, *Organic Reactions*, Vol. VI, p. 97.
[7] Kondo and Ishiwata, *Ber.*, 1931, **64**, 1533.
[8] Callow, Gulland, and Haworth, *J.*, 1929, 1444.
[9] Govindachari and Nagarajan, *Chem. and Ind.*, 1954, 1358.
[10] Hey and Palluel, *Chem. and Ind.*, 1955, 40.

R = NH·CH_2·CH_2Ph) of 6 : 7-dimethoxyanthranil-3-carboxylic acid (4 : 5-dimethoxyanthroxanic acid).

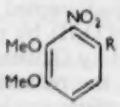
The evidence for this structure is based on the fact that hydrolysis of the neutral compound with acid gave phenethylamine, whereas hydrolysis with alcoholic potassium hydroxide gave some phenethylamine and 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = OH). If the neutral compound had either the keten-imine structure or the



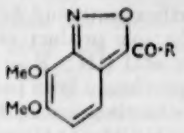
(I)



(II)



(III)



(IV)

acetylenic structure, hydrolysis would lead to 3 : 4-dimethoxy-2-nitrophenylacetic acid. This acid was never found. Further, reduction of the neutral compound with zinc and hydrochloric acid gave the phenethylamide of 2-amino-3 : 4-dimethoxyphenylglyoxylic acid (2 : 3-dimethoxyisatinic acid). On the alternative formulations reduction should lead to 2-(2-amino-3 : 4-dimethoxyphenyl)-2-phenylethylamine. The identity of the 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = OH) has been confirmed by two independent syntheses of this acid (*a*) from 3 : 4-dimethoxy-2-nitrophenylacetic acid by Gulland's method [11] and (*b*) from 3 : 4-dimethoxy-2-nitromandelic acid by the method of Gulland, Robinson, Scott, and Thornley.[12] The identity of the three acids has been further confirmed by infrared and ultraviolet spectroscopy. The synthetic acid thus obtained has also been converted into its phenethylamide, which was shown to be identical with the neutral product obtained in the application of the Bischler–Napieralski reaction to 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide. The isolation of 6 : 7-dimethoxyanthranil-3-carboxylic acid on alkaline hydrolysis of the neutral compound is not in itself proof of the anthranil structure for the neutral compound because 3 : 4-dimethoxy-2-nitrophenylacetic acid also gives the anthranil-carboxylic acid on treatment with alkali, but the synthesis of the neutral compound from 6 : 7-dimethoxyanthranil-3-carboxylic acid, as reported above, establishes its structure beyond all doubt.

When 3 : 4-dimethoxy-2-nitrophenyl-*N*-*iso*propylacetamide (III; R = CH_2·CO·NHPr^i), which cannot undergo the Bischler–Napieralski reaction, was boiled in benzene solution with phosphorus pentachloride, the *iso*propylamide of 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = NHPr^i) was obtained in good yield. The ultraviolet absorption spectrum of this compound showed bands of maximum absorption at 237·5 and 295 mμ, identical with those observed for 6 : 7-dimethoxyanthranil-3-carboxylic acid and the neutral compound from the Bischler–Napieralski reaction.

The infrared spectrum of the neutral compound from the Bischler–Napieralski reaction indicates the presence of an amide group and shows the complete absence of significant absorption between the C–H stretching frequencies at 3·46 μ and a strong absorption band at 6·00 μ. Since it is precisely in this region that the characteristic absorption bands of the triple carbon–carbon bond (4·5—5·1 μ) and of the keten-imine structure (4·87—5·00 μ), as reported by Stevens and French,[13] reside, it is reasonable to assume that these structural features are absent. The ultraviolet spectrum also shows the absence of the keten-imine structure (cf. Stevens and French [13]).

The formation of anthranils (3 : 4-benz*iso*oxazoles) by *cyclo*dehydration of aromatic compounds containing a nitro-group and a methylene group at adjacent nuclear positions is well known. Anthranil itself is formed from *o*-nitrotoluene on treatment with alkali,[14]

[11] Gulland, *J.*, 1931, 2872.
[12] Gulland, Robinson, Scott, and Thornley, *J.*, 1929, 2924.
[13] Stevens and French, *J. Amer. Chem. Soc.*, 1953, **75**, 657; 1954, **76**, 4398.
[14] Scholl, *Monatsh.*, 1913, **34**, 1016.

and phenylanthranil can be obtained when *o*-nitrodiphenylmethane is heated alone or in the presence of aluminium chloride or sulphuric acid.[15] Similar compounds can also be obtained by the mild reduction of a nitro-group which is *ortho* to a carbonyl group, *e.g.*, *o*-nitrobenzaldehyde and *o*-nitroacetophenone. Anthranil-3-carboxylic acid has been prepared (*a*) by the action of heat on *o*-nitroepoxycinnamic acid,[16] (*b*) by the mild reduction of *o*-nitromandelic acid or nitrile,[17] and (*c*) from *o*-nitrophenylacetic acid by mild reduction and cyclisation to 1 : 2-dioxindole followed by treatment with nitrous acid and rearrangement under acidic conditions.[18] When reduced with ferrous sulphate and ammonia anthranil-3-carboxylic acid gives isatinic acid and then isatin by *cyclo*dehydration. 6 : 7-Dimethoxyanthranil-3-carboxylic acid (IV; R = OH) was reported by Gulland [11] to be the sole product of the attempted demethylation of 3 : 4-dimethoxy-2-nitrophenylacetic acid (III; R = $CH_2 \cdot CO_2H$) by prolonged boiling with alkali. A similar product had previously been isolated by Gulland, Robinson, Scott, and Thornley,[12] together with 6 : 7-dimethoxyisatin, from the reduction of 3 : 4-dimethoxy-2-nitromandelic acid [III; R = $CH(OH) \cdot CO_2H$] with sodium amalgam, but this compound was provisionally formulated as a derivative of azobenzene. The reaction of 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = OH) with ferrous sulphate and ammonia gives 6 : 7-dimethoxyisatin.

The identity of the 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (II) was confirmed by conversion into the methiodide, followed by reduction to 1-(2-amino-3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline, which was characterised as the dipicrolonate, with subsequent diazotisation and ring closure by the Pschorr procedure to give (±)-*apo*morphine dimethyl ether (I). The latter was characterised as the hydrochloride and methiodide and the ultraviolet absorption spectrum of the hydrochloride was identical with that of (−)-*apo*morphine dimethyl ether hydrochloride prepared from (−)-*apo*morphine hydrochloride. Späth and Hromatka [1] identified their synthetic racemic *apo*morphine dimethyl ether with the corresponding compound obtained from the natural product by the conversion of both into *N*-benzoyl-β-(5 : 6-dimethoxyphenanthryl)-*N*-methylethylamine. Attempts made by Späth and Hromatka to racemise (−)-*apo*morphine dimethyl ether were unsuccessful.

When a solution of 2-nitrophenyl-*N*-phenethylacetamide was boiled in toluene solution in the presence of phosphoric oxide it gave an unidentified brown gum as the main product, but 3 : 4-dihydro-1-(2-nitrobenzyl)*iso*quinoline was isolated in small yield.

Experimental

Application of the Bischler–Napieralshi Reaction to 3 : 4-*Dimethoxy*-2-*nitrophenyl*-N-*phenethylacetamide.*—(a) *With phosphoric oxide.* A solution of the amide (3 g.; Hey and Lobo [5]) in toluene (50 c.c.) was added to a suspension of phosphoric oxide (18 g.) in toluene (50 c.c.), and the mixture was boiled under reflux for 1 hr. The toluene was separated by decantation and the residual solid cake was broken up and washed twice by decantation with boiling benzene. Evaporation of the combined toluene and benzene solutions left a crystalline residue (0·62 g.), which on crystallisation from methanol gave 6 : 7-*dimethoxy*-N-*phenethylanthranil*-3-*carboxyamide* in fine yellow needles, m. p. 123—124° (Found: C, 66·1; H, 5·6; N, 8·8. $C_{18}H_{18}O_4N_2$ requires C, 66·2; H, 5·5; N, 8·6%). This compound was insoluble in dilute and concentrated hydrochloric acid and failed to yield a picrate. After being boiled with zinc and hydrochloric acid the resulting solution was capable of diazotisation and the diazonium solution gave a bright orange precipitate with alkaline β-naphthol. Kay and Pictet [3] reported m. p. 129° for this neutral compound. Späth and Hromatka [1] reported 124—126° and Hey and Lobo [5] m. p. 124—125°. The solid residue containing phosphoric oxide was decomposed with ice and dilute hydrochloric acid, and the aqueous solution was extracted once with benzene and several times with chloroform. Evaporation of the chloroform extracts left white crystals (0·64 g.), which on recrystallisation from ethanol containing a drop of concentrated hydrochloric acid gave the *hydrochloride* of 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline in fine needles, m. p. 220—221° (Found: C, 59·55; H, 5·4; N, 7·5. $C_{18}H_{18}O_4N_2$,HCl requires C, 59·5; H, 5·5;

[15] Kliegl, *Ber.*, 1909, **42**, 591.
[16] Schillinger and Wleügel, *Ber.*, 1883, **16**, 2226.
[17] Heller, *Ber.*, 1906, **39**, 2344.
[18] Reissert, *Ber.*, 1908, **41**, 3921.

N, 7·9%). In a second experiment the amide (1 g.) gave **6** : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·22 g.) in yellow needles (from ethanol), m. p. 123—124°, and, by ether-extraction of the basified aqueous solution, 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (0·26 g.), m. p. 115—121°, as a buff amorphous solid from aqueous methanol. Späth and Hromatka [1] reported m. p. 129° for this base. The *picrate*, prepared in the normal manner, separated from methanol in yellow-brown needles m. p. 166—167° (Found : C, 51·6; H, 4·0. $C_{18}H_{18}O_4N_2,C_6H_3O_7N_3$ requires C, 51·9; H, 3·8%). A solution of the free base (0·52 g.) in methanol (15 c.c.) was boiled under reflux for 2 hr. with methyl iodide (7 c.c.). Subsequent evaporation of the solvent and excess of methyl iodide left 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline methiodide (0·44 g.) in fine yellow needles, m. p. 200° (from ethanol) (Found : I, 27·2. Calc. for $C_{19}H_{21}O_4N_2I$: I, 28·1%). The same methiodide was obtained from the free base isolated from the hydrochloride of m. p. 220—221°. Späth and Hromatka [1] recorded m. p. 203° for the methiodide.

(b) *With phosphorus pentachloride.* A solution of the amide (1·7 g.) in benzene (30 c.c.), added to a suspension of phosphorus pentachloride (1 g.) in benzene (30 c.c.), was boiled under reflux. Evolution of hydrogen chloride ceased after 1 hr. and the solvent and phosphorus oxychloride were removed under reduced pressure. Recrystallisation of the crystalline residue from benzene–light petroleum (b. p. 60—80°) gave **6** : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·95 g.) in yellow needles, m. p. 121—123°, both alone and on admixture with the neutral compound prepared by method (*a*) above.

Hydrolysis of **6** : 7-*Dimethoxy*-N-*phenethylanthranil*-3-*carboxyamide*.—(a) *With hydrochloric acid.* **6** : 7-Dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·2 g.) was boiled under reflux with 10% hydrochloric acid (50 c.c.) for 24 hr. The yellow solution was decanted from solid matter, cooled, and extracted with ether. Evaporation of the ether left a residue (0·06 g.) from which no crystalline product could be obtained. The aqueous solution, made alkaline with sodium hydroxide, was shaken with a few drops of benzoyl chloride. *N*-Phenethylbenzamide separated, which after recrystallisation from ethanol had m. p. and mixed m. p. 111—112°.

(b) *With alcoholic potassium hydroxide.* A solution of **6** : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·8 g.) in ethanol (100 c.c.) was boiled under reflux with a solution of potassium hydroxide (20 g.) in ethanol (200 c.c.) for 5 hr. The solution was diluted with water, and most of the alcohol was removed by distillation. The cold aqueous solution was extracted with ether, and the ethereal extract was washed with dilute hydrochloric acid. The acidic washings were shown to contain phenethylamine (0·08 g.) by conversion into *N*-phenethylbenzamide, m. p. 111—112°, as described above. The aqueous alkaline solution was acidified with hydrochloric acid, and on cooling and standing a crystalline acid was deposited (0·2 g.), which on recrystallisation, first from hot water and then from benzene, gave **6** : 7-dimethoxyanthranil-3-carboxylic acid in bright orange needles, m. p. 166—167° (Found : C, 53·4; H, 4·3; N, 6·4. Calc. for $C_{10}H_9O_5N$: C, 53·7; H, 4·0; N, 6·3%). The m. p. was not depressed on admixture with specimens of this acid prepared as described below.

Reduction of **6** : 7-*Dimethoxy*-N-*phenethylanthranil*-3-*carboxyamide*.—(a) *Catalytic.* No hydrogen was absorbed when the amide in methanol–benzene was shaken with palladium on barium sulphate or Adams's catalyst.

(b) *With zinc and hydrochloric acid.* To an ice-cold solution of **6** : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·1 g.) in ethanol (20 c.c.) was added concentrated hydrochloric acid (0·5 c.c.) and zinc dust (0·1 g.) portionwise with agitation. Further small quantities of zinc dust and of concentrated hydrochloric acid, one drop at a time, were added until the solution was colourless. The solution was made alkaline with aqueous ammonia and extracted four times with ether. Evaporation of the extract left a crystalline residue (0·1 g.), which on recrystallisation from ether gave the *phenethylamide* of 2-*amino*-3 : 4-*dimethoxyphenylglyoxylic acid* in needles, m. p. 92—93° (Found : C, 65·4; H, 6·4. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1%). This product gave a positive reaction on diazotisation and coupling with alkaline β-naphthol. The same product was obtained in 60% yield on reduction of the amide with zinc and sulphuric acid.

Anthranil-3-*carboxylic Acid* (*Anthroxanic Acid*).—Anthranil-3-carboxylic acid [needles from hot water; m. p. 196° (decomp.)] (Found : C, 58·5; H, 3·0. Calc. for $C_8H_5O_3N$: C, 58·8; H, 3·0%) was prepared from *o*-nitrophenylacetic acid (Marion and Grassie [19]) by Reissert's method [18] by means of 1 : 2-dioxindole (white needles, m. p. 199—201°, from hot water) (Found : C, 64·0; H, 4·7. Calc. for $C_8H_7O_2N$: C, 64·4; H, 4·7%), and 1-hydroxyisatoxime [yellow amorphous solid from hot water; m. p. 230—231° (decomp.)] (Found : C, 53·8; H, 3·3. Calc.

[19] Marion and Grassie, *J. Amer. Chem. Soc.*, 1944, **66**, 1290.

for $C_8H_6O_3N_2$: C, 53·8; H, 3·4%). Reissert gave no m. p. for 1 : 2-dioxindole but reported m. p. 223° for 1-hydroxyisatoxime, and m. p. 196° for anthranil-3-carboxylic acid. For the latter acid Heller [17] reported m. p. 200° and Schillinger and Wleügel [16] m. p. 190—191°. Anthranil-3-carboxylic acid was also obtained in much poorer yield from the reduction of *o*-nitromandelonitrile by Heller's method.[17] Attempts to apply Gulland's method [11] for the preparation of 6 : 7-dimethoxyanthranil-3-carboxylic acid to the preparation of anthranil-3-carboxylic acid from *o*-nitrophenylacetic acid failed. When a solution of anthranil-3-carboxylic acid (0·2 g.) in a slight excess of aqueous ammonia was added to a solution of ferrous sulphate (1 g.) in water and boiled under reflux for 3 hr., subsequent filtration and acidification gave isatin in red needles (0·13 g.), m. p. and mixed m. p. 199—200°.

6 : 7-*Dimethoxyanthranil-3-carboxylic Acid.*—This acid [orange needles from benzene; m. p. 168—169° (decomp.)] was prepared from 3 : 4-dimethoxy-2-nitrophenylacetic acid in 31% yield by Gulland's method.[11] It was also obtained in poorer yield from 3 : 4-dimethoxy-2-nitromandelic acid by the method of Gulland, Robinson, Scott, and Thornley.[12] The acid (0·5 g.) in a slight excess of aqueous ammonia (100 c.c.) was added to ferrous sulphate (2·5 g.) in water (50 c.c.) and boiled under reflux for 3 hr. After filtration of the hot solution the cold filtrate was extracted with chloroform, evaporation of which gave 6 : 7-dimethoxyisatin (0·33 g.) in orange needles (from ethanol), m. p. 209—210° (Found : C, 58·3; H, 4·5. Calc. for $C_{10}H_9O_4N$: C, 58·0; H, 4·4%). Gulland, Robinson, Scott, and Thornley [12] gave m. p. 212—213° for this compound. The semicarbazone, prepared in the normal manner, was obtained in pale yellow platelets, m. p. 254° (decomp.), from aqueous alcohol, as recorded by Gulland *et al.*[12]

6 : 7-*Dimethoxy-N-phenethylanthranil-3-carboxyamide.*—6 : 7-Dimethoxyanthranil-3-carboxylic acid (0·45 g.) was added portionwise to a suspension of phosphorus pentachloride (0·42 g.) in chloroform (30 c.c.). After having been shaken mechanically overnight at room temperature, the mixture was boiled under reflux until a clear solution was obtained (48 hr.). Evaporation of the solvent and phosphorus oxychloride under reduced pressure left a red solid, which was dissolved in boiling ether (50 c.c.). To the boiling solution was added a solution of phenethylamine (1 g.) in dry ether (20 c.c.). After boiling under reflux for 2 hr. the whole was added to water (100 c.c.), and the ethereal layer separated. The aqueous layer was extracted several times with ether and the combined ethereal extracts were washed successively with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water, dried, and evaporated. The crystalline residue (0·33 g.) gave 6 : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide in yellow needles, m. p. 121·5—122·5°, from methanol. A mixed m. p. with the neutral product, m. p. 123—124°, obtained from the Bischler–Napieralski reactions with 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide, showed no depression. The infrared and ultraviolet absorption spectra of this compound showed the absence of keten-imine and acetylenic structures.

3 : 4-*Dimethoxy-2-nitrophenyl-N-isopropylacetamide.*—3 : 4-Dimethoxy-2-nitrophenylacetic acid (2 g.) was added portionwise to a suspension of phosphorus pentachloride (2·2 g.) in dry chloroform (15 c.c.), and the mixture was set aside with occasional shaking until a homogeneous solution was obtained. Evaporation of the solvent and phosphorus oxychloride under reduced pressure left the acid chloride in fine needles, which were dissolved in dry ether (50 c.c.) and added with cooling to a solution of *iso*propylamine (5 g.) in ether (20 c.c.). After boiling under reflux for 1 hr. the mixture was added to an excess of dilute hydrochloric acid, and the ethereal layer was separated. The aqueous layer was further extracted with ether and the combined ethereal solution was washed successively with dilute acid, dilute alkali, and water. Evaporation of the dried solvent left 3 : 4-*dimethoxy-2-nitrophenyl-N-isopropylacetamide* (2·1 g.), which crystallised from benzene–light petroleum (b. p. 60—80°) in buff needles, m. p. 103—104° (Found : C, 55·7; H, 6·6. $C_{13}H_{18}O_5N_2$ requires C, 55·5; H, 6·4%).

6 : 7-*Dimethoxy-N-isopropylanthranil-3-carboxyamide.*—A solution of 3 : 4-dimethoxy-2-nitrophenyl-*N-iso*propylacetamide (1 g.) in dry benzene (50 c.c.) was boiled under reflux for 1 hr. with phosphorus pentachloride (0·7 g.). Evaporation of the solvent and phosphorus oxychloride left a yellow oil, which was dissolved in benzene and chromatographed on an alumina column. Evaporation of the benzene eluates left 6 : 7-*dimethoxy-N-isopropylanthranil-3-carboxyamide* as a crystalline residue (0·7 g.), which separated from aqueous ethanol in yellow platelets, m. p. 92—93° (Found : C, 59·2; H, 6·1. $C_{13}H_{16}O_4N_2$ requires C, 59·9; H, 6·1%). The ultraviolet absorption spectrum of this compound showed bands at 237·5 and 295 mμ, identical with those observed in 6 : 7-dimethoxyanthranil-3-carboxylic acid and its phenethylamide.

(±)-apo*Morphine Dimethyl Ether*.—A suspension of 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline methiodide (0·8 g.) (prepared as described above) in ethanol (30 c.c.) was boiled under reflux for 0·5 hr. with concentrated hydrochloric acid (15 c.c.) and zinc dust (4 g.). The colour of the solution changed from yellow to green and was finally discharged. A sample of the solution gave a positive reaction on diazotisation and addition to alkaline β-naphthol. The cooled filtered solution was extracted with ether, and the aqueous layer was then made alkaline with aqueous sodium hydroxide and repeatedly extracted with ether. Evaporation of the ether gave 1-(2-amino-3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline (0·5 g.) as a pale brown oil with a blue fluorescence. The *dipicrolonate*, formed in ethanol in the normal manner, separated from a large volume of ethanol in orange-yellow needles, m. p. 189—190° (Found : C, 55·35; H, 4·9; N, 16·8. $C_{19}H_{24}O_2N_2,2C_{10}H_8O_5N_4$ requires C, 55·7; H, 4·8; N, 16·7%). A suspension of this dipicrolonate (1·5 g.) in cold methanol (7·5 c.c.) was ground with a cold solution of concentrated sulphuric acid (1·5 c.c.) in methanol (7·5 c.c.). The precipitated picrolonic acid (0·89 g.) was filtered off and the filtrate was cooled to 0° and diazotised with a solution of sodium nitrite (0·123 g.) in water (2 c.c.). After 12 hr. in the refrigerator, copper powder was added and nitrogen was evolved. After 1 hr. the mixture was boiled under reflux, filtered, cooled, diluted with water, made alkaline with ammonia, and extracted with ether. The brown residue obtained on evaporation was dissolved in hydrochloric acid and extracted successively with ether and chloroform. (±)-apo*Morphine dimethyl ether hydrochloride*, obtained from the chloroform extract on evaporation, crystallised from ethanol–ether in fine needles (0·1 g.), m. p. 212—218° (decomp.) (Found : C, 66·6; H, 6·7. $C_{19}H_{21}O_2N,HCl,\frac{1}{2}H_2O$ requires C, 66·8; H, 6·7%). A portion of the hydrochloride (0·02 g.) in water was neutralised with aqueous ammonia and extracted with ether. Evaporation of the dried extract gave DL-*apo*morphine dimethyl ether as a pale brown gum, which was dissolved in dry chloroform to which an excess of methyl iodide (5 c.c.) was added. (±)-apo*Morphine dimethyl ether methiodide* separated, m. p. 218—220° (decomp.) (Found : C, 54·0; H, 5·7; N, 3·1 $C_{20}H_{24}O_2NI,\frac{1}{2}H_2O$ requires C, 53·8; H, 5·6; N, 3·1%). For comparison a specimen of (−)-*apo*-morphine dimethyl ether hydrochloride was prepared from *apo*morphine hydrochloride B.P. by methylation with diazomethane. It separated from ethanol–ether in needles, m. p. 220—225° (Found : C, 66·7; H, 6·4. Calc. for $C_{19}H_{21}O_2N,HCl,\frac{1}{2}H_2O$: C, 66·8; H, 6·7%). (−)-*apo*-Morphine dimethyl ether methiodide, prepared from the hydrochloride as described above for the racemic compound, had m. p. 210—212° (decomp.) (Found : C, 54·0; H, 5·6; N, 3·1. Calc. for $C_{20}H_{24}O_2NI,\frac{1}{2}H_2O$: C, 53·8; H, 5·6; N, 3·1%). Pschorr, Jaeckel, and Fecht [10] recorded the preparation of (−)-*apo*morphine dimethyl ether hydrochloride but gave no m. p. The same authors reported m. p. 195—205° for the methiodide. The ultraviolet absorption spectrum of the (±)-*apo*morphine dimethyl ether hydrochloride and that of the (−)-form were indistinguishable.

3 : 4-*Dihydro*-1-2′-*nitrobenzylisoquinoline*.—A solution of *o*-nitrophenyl-*N*-phenethylacetamide (1 g.; Hey and Lobo [5]) in dry toluene (30 c.c.), added to a suspension of phosphoric oxide (6 g.) in toluene (20 c.c.), was boiled under reflux for 17 hr., further quantities of phosphoric oxide (4 g.) being added during the first 2 hr. The solvent was separated by decantation and the solid matter was washed three times by decantation with hot toluene (150 c.c.). The residual solid was treated with crushed ice (100 g.) and concentrated hydrochloric acid (10 c.c.), and the mixture was heated to boiling and then cooled and repeatedly extracted with benzene. Evaporation of the combined toluene and benzene solution gave a dark brown gum (0·41 g.). The aqueous acid solution was filtered (charcoal), made alkaline with aqueous sodium hydroxide, and extracted with ether. Evaporation of the dried ethereal extract left a red gum, which solidified on trituration with methanol. 3 : 4-Dihydro-1-2′-nitrobenzyl*iso*quinoline (0·23 g.) separated from methanol as a pale buff amorphous solid, m. p. 115—116°. The *picrate*, prepared in the normal manner, separated from methanol in fine yellow needles, m. p. 186—187° (Found : C, 53·2; H, 3·3. $C_{16}H_{14}O_2N_2,C_6H_3O_7N_3$ requires C, 53·3; H, 3·4%). The methiodide separated from ethanol in yellow needles, m. p. 215—216° (decomp.). Govindachari and Nagarajan [9] reported m. p. 115—116° for 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinoline and m. p. 209° (decomp.) for the methiodide.

Spectroscopic measurements were carried out on a Unicam S.P. 500 quartz spectrometer and on a Grubb-Parsons double-beam infrared spectrometer.

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[10] Pschorr, Jaeckel, and Fecht, *Ber.*, 1902, **35**, 4387.

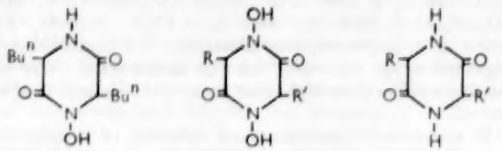
797. *Pulcherrimin: A Synthesis of 1:4-Dihydroxy-2:5-dioxopiperazines.**

By A. H. Cook and C. A. Slater.

Following earlier studies,[1,2,3] representative α-hydroxyamino-acids, prepared by a new method, were converted into the corresponding substituted 1:4-dihydroxy-2:5-dioxopiperazines (II). However, 2:5-di*iso*butyl-1:4-dihydroxy-3:6-dioxopiperazine (II; R = R′ = Bu^{i}) proved, contrary to the earlier indications, to be different from the parent acid [3] of the yeast pigment pulcherrimin, the structure of which accordingly requires revision.

Van der Walt [1] and, in particular, Kluyver, van Triet, and van der Walt [2] suggested that pulcherrimin, a pigment produced by the yeast *Candida pulcherrima* (Lindner) Windisch, was an iron complex of 2:5-di*iso*butyl-1:4-dihydroxy-3:6-dioxopiperazine. This suggestion was supported by later more detailed work,[3] and synthesis of the pigment was therefore undertaken. As no synthetic compounds of this type had been reported, it was first desirable to devise a general synthesis of substituted 1:4-dihydroxy-2:5-dioxopiperazines. This was accomplished by a route which paralleled the synthesis of 2:5-dioxopiperazines from (bromoacylamino)-esters,[4] but which started from relevant α-hydroxyamino-acids instead of α-amino-acids.

Although individual α-hydroxyamino-acids have from time to time been prepared [5] the methods usually proved troublesome. In addition, little is known of the general nature of these compounds. The required intermediates were, however, in the present work obtained conveniently in about 50% yield by treating the appropriate α-bromo-acid with methanolic hydroxylamine. α-Hydroxyamino-*iso*valeric, -hexanoic, and -γ-methylvaleric acids were prepared in this way. These compounds proved to be weak acids without marked basic properties. They were strong reducing agents and on oxidation afforded



(I) (II) (III)

the lower homologous aldehyde. Reduction gave the corresponding amino-acid together with about 10% of the corresponding dioxopiperazine (III; R = R′ = Pr^{i}, Bu^{n}, or Bu^{i}). Pyrolysis yielded a mixture of products including ammonia, carbon dioxide, the corresponding amino-acid, and the lower homologous aldehyde. Attempts to prepare the *p*-bromophenacyl, *p*-nitrobenzyl, and *p*-phenylphenacyl esters by the usual techniques were unsuccessful but the methyl and the *n*-butyl esters were obtained crystalline whilst the ethyl esters were high-boiling liquids. Diazomethane reacted rapidly with α-hydroxyamino-γ-methylvaleric acid and gave by *N*-methylation as well as esterification methyl α-(*N*-hydroxy-*N*-methylamino)-γ-methylvalerate.

The methyl α-hydroxyamino-esters were more basic than the parent acids and possessed similar strong reducing properties. Methyl 2-hydroxyaminohexanoate was characterised

* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Van der Walt, *Proefsch. Tech. Hoges., Delft*, 1952.
[2] Kluyver, van Triet, and van der Walt, *Proc. Nat. Acad. Sci., U.S.A.*, 1953, **39**, 583.
[3] Cook and Slater, *J. Inst. Brewing*, 1954, **60**, 213.
[4] Dunn, Gallagher, Newbold, and Spring, *J.*, 1949, 5130.
[5] Miller and Plöchl, *Ber.*, 1892, **25**, 2020; Traube, *ibid.*, 1895, **28**, 2300; Steiger, *J. Biol. Chem.*, 1944, **153**, 691; Snow, *J.*, 1954, 2594.

as its crystalline benzoyl derivative and as a low-melting chloroacetyl derivative. Other acyl derivatives were prepared as syrups. All these acyl compounds gave red colours with methanolic ferric chloride indicating that *N*- and not *O*-acylation had taken place.

Treatment of methyl 2-(*N*-2-bromohexanoyl-*N*-hydroxyamino)hexanoate with ammonia gave a compound, $C_{12}H_{22}O_3N_2$, which can be reasonably formulated only as (I) (cf. Dunn *et al.*[4]). Parallel reactions between hydroxylamine and methyl 2-(*N*-2-bromohexanoyl-*N*-hydroxyamino)hexanoate or methyl α-[*N*-(α-bromo-γ-methylvaleryl-*N*-hydroxyamino)]-γ-methylvalerate gave compounds which, by analogy in conjunction with the analytical evidence, are acceptably formulated as (II; R = R′ = Bu^n or Bu^i). Similarly the action of hydroxylamine on methyl 2-(*N*-chloroacetyl-*N*-hydroxyamino)-hexanoate or the γ-methylvaleryl analogue gave (II; R = H, R′ = Bu^n or Bu^i).

These representations are further supported by the fact that the compounds (II; R = R′ = Bu^n or Bu^i) give on reduction the corresponding 2 : 5-dioxopiperazines (III; R = R′ = Bu^n or Bu^i). Moreover, these compounds are weakly acidic, as would be expected, and analysis of representative methyl esters showed that each of the latter contained two methoxyl groups. In common with all hydroxamic acids, the 1 : 4-dihydroxy-2 : 5-dioxopiperazines give red colours with methanolic ferric chloride and insoluble copper complexes with methanolic cupric acetate.

2 : 5-Di*iso*butyl-1 : 4-dihydroxy-3 : 6-dioxopiperazine so synthesised differed markedly from pulcherriminic acid, the parent acid of pulcherrimin,[3] despite earlier degradative evidence. For instance, it has m. p. 253° (decomp.) whereas pulcherriminic acid has m. p. 171°. Unlike the compound from natural sources, it is not readily methylated by diazomethane, fails to give characteristic *cyclo*hexylamine or morpholine salts, and gives no precipitate but only a red colour with methanolic ferric chloride. For these reasons the structure previously given for pulcherriminic acid and for pulcherrimin [3] must be rejected.

Experimental

*α-Hydroxyamino*isovaleric *Acid*.—α-Bromo*iso*valeric acid (40 g.) was neutralised at 0° with methanolic sodium methoxide and then treated with a solution of hydroxylamine prepared as follows: Hydroxylamine hydrochloride (27·6 g.) was dissolved in warm methanol (200 c.c.) and treated with methanolic sodium methoxide from sodium (9·2 g.) and methanol (100 c.c.) with cooling; the mixture was cooled in ice and the precipitated sodium chloride removed. The mixture was heated under reflux overnight, then evaporated, and the residue treated with water. Recrystallisation of the insoluble product from water gave *α-hydroxyaminoisovaleric acid* (2·7 g., 10%), m. p. 204° (decomp.) (Found: C, 45·4; H, 8·4; N, 10·7. $C_5H_{11}O_3N$ requires C, 45·2; H, 8·3; N, 10·5%). Similarly were obtained *2-hydroxyaminohexanoic acid* (46%), prisms, m. p. 161—162° (decomp.), from aqueous ethanol (Found: C, 49·3; H, 9·2; N, 9·4. $C_6H_{13}O_3N$ requires C, 49·0; H, 8·8; N, 9·5%), and *α-hydroxyamino-γ-methylvaleric acid* (44%) (from aqueous ethanol), plates, m. p. 155° (decomp.) (Found: C, 48·9; H, 8·8; N, 9·5%).

Reduction. Zinc dust (0·3 g.) was added during 1 hr. to a solution of α-hydroxyamino-γ-methylvaleric acid (0·5 g.) in acetic acid (10 c.c.) heated under reflux. The solution was filtered, diluted with water (10 c.c.), and adjusted to pH 6 with aqueous ammonia. Recrystallisation of the product (0·05 g.) from water gave needles, m. p. 268° alone or on admixture with 2 : 5-di*iso*butyl-3 : 6-dioxopiperazine. The residual acetic acid solution above was shown by paper chromatography to contain leucine.

Oxidation. The same hydroxyamino-acid (0·5 g.) in saturated aqueous sodium hydrogen carbonate was treated with a slight excess of aqueous potassium permanganate. The solution was distilled into aqueous 2 : 4-dinitrophenylhydrazine hydrochloride, and the dinitrophenylhydrazone was chromatographed in benzene on alumina. Recrystallisation of the product from ethanol gave *iso*valeraldehyde 2 : 4-dinitrophenylhydrazone (0·2 g.) as plates, m. p. and mixed m. p. 123°.

Reaction with diazomethane. The same hydroxyamino-acid (0·5 g.) with diazomethane (0·6 g.) in ether gave *methyl α-(N-hydroxy-N-methylamino)-γ-methylvalerate* (0·2 g.) as a colourless oil, b. p. 104°/6 mm. (Found: C, 55·2; H, 9·6; N, 7·6; MeO, 19·4. $C_8H_{17}O_3N$ requires C, 54·9; H, 9·7; N, 8·0; MeO, 17·7%).

Methyl 2-Hydroxyaminohexanoate.—2-Hydroxyaminohexanoic acid (10 g.) was suspended

in methanol (50 c.c.) and was treated cautiously, with stirring, with concentrated sulphuric acid (25 c.c.). The whole was set aside overnight. The solution was poured into water (200 c.c.), and excess of solid sodium carbonate added. The *methyl ester* was extracted with ether and was obtained as an almost colourless, crystalline solid (10·6 g., 96·3%). Recrystallised from light petroleum it formed needles, m. p. 55° (Found : C, 52·2; H, 9·3; N, 8·8. $C_7H_{15}O_3N$ requires C, 52·1; H, 9·3; N, 8·7). The following were prepared similarly : *Methyl* (64%), needles, m. p. 51°, from light petroleum (Found : C, 52·2; H, 9·1; N, 8·8%), and n-*butyl* α-*hydroxyamino*-γ-*methylvalerate* (from aqueous ethanol), needles, m. p. 60° (Found : C, 59·3; H, 10·5; N, 6·4. $C_{10}H_{21}O_3N$ requires C, 59·1; H, 10·4; N, 6·9%); *ethyl*, b. p. 90—95°/0·2 mm. (Found : C, 54·7; H, 9·7; N, 7·7. $C_8H_{17}O_3N$ requires C, 54·8; H, 9·7; N, 8·0%), and n-*butyl* 2-*hydroxyaminohexanoate*, b. p. 110—120°/0·1 mm. (Found : C, 59·4; H, 10·4; N, 6·6%); *ethyl* α-*hydroxyamino*-γ-*methylvalerate*, b. p. 90—95°/0·2 mm. (Found : C, 54·9; H, 9·7; N, 7·7%).

Acylation. Methyl 2-hydroxyaminohexanoate (0·5 g.) was boiled with acetic anhydride (0·5 c.c.) for 5 min. Distillation gave the *acetyl derivative* (0·2 g.), b. p. 104—104°/1·5 mm. (Found : C, 53·0; H, 8·5; N, 6·8. $C_9H_{17}O_4N$ requires C, 53·2; H, 8·4; N, 6·9%).

Methyl 2-hydroxyaminohexanoate (1 g.) in dry chloroform (10 c.c.) was treated with benzoyl chloride (0·5 c.c.) and set aside for 30 min. The solution was shaken successively with aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water until neutral. Evaporation of the chloroform gave the *benzoyl derivative* (0·4 g.) which recrystallised from light petroleum–benzene (10 : 1 v/v) in needles, m. p. 76° (Found : C, 63·2; H, 7·3; N, 5·1. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; N, 5·2%). The following were prepared similarly : *Methyl* 2-(N-*chloroacetyl*-N-*hydroxyamino*)*hexanoate* which recrystallised from light petroleum in needles, m. p. 55° (Found : C, 45·6; H, 6·9; N, 5·3; Cl, 14·4. $C_9H_{16}O_4NCl$ requires C, 45·4; H, 6·7; N, 5·9; Cl, 14·9%); *methyl* α-(N-*chloroacetyl*-N-*hydroxyamino*)-γ-*methylvalerate*, m. p. 81° (Found : C, 45·2; H, 6·8; N, 5·7; Cl, 15·0%); *methyl* 2-(N-2-*bromohexanoyl*-N-*hydroxyamino*)*hexanoate*, b. p. 125—130°/0·01 mm. (Found : C, 46·3; H, 7·3; N, 4·2; Br, 24·0. $C_{13}H_{24}O_4NBr$ requires C, 46·2; H, 7·1; N, 4·1; Br, 23·7%); and *methyl* α-[N-(α-*bromo*-γ-*methylvaleryl*)-N-*hydroxyamino*]-γ-*methylvalerate*, b. p. 135—140°/10^{-3} mm. (Found : C, 46·2; H, 7·3; N, 4·0; Br, 24·6%). All these acyl derivatives gave red colours with methanolic ferric chloride.

2 : 5-*Di*-n-*butyl*-1-*hydroxy*-3 : 6-*dioxopiperazine*.—Methyl 2-(N-2-bromohexanoyl-N-hydroxyamino)hexanoate (0·4 g.) and saturated ethanolic ammonia (15 c.c.) were mixed and kept for 48 hr. Dilution with water followed by recrystallisation of the product (0·2 g.) from ethyl acetate gave the *piperazine* as plates, m. p. 187—190° (decomp.) (Found : C, 59·6; H, 9·1; N, 11·6. $C_{12}H_{22}O_3N_2$ requires C, 59·5; H, 9·1; N, 11·6%).

3-n-*Butyl*-1 : 4-*dihydroxy*-2 : 5-*dioxopiperazine*.—Methyl 2-(N-chloroacetyl-N-hydroxyamino)-hexanoate (1 g.) was kept with excess of methanolic hydroxylamine overnight; the *piperazine* (0·09 g.) separated. Evaporation of the mother-liquor gave a further crop (0·09 g.). Recrystallisation from ethyl acetate gave needles, m. p. 214° (decomp.) (Found : C, 47·6; H, 6·8; N, 13·4. $C_8H_{14}O_4N_2$ requires C, 47·6; H, 6·9; N, 13·8%). The following were prepared similarly : 3-iso*butyl*-1 : 4-*dihydroxy*-2 : 5-*dioxopiperazine* (from ethanol), needles, m. p. 235—236° (decomp.) (Found : C, 47·4; H, 6·9; N, 13·8%), and 2 : 5-*di*-n-*butyl*- (from ethyl acetate), needles, m. p. 232—233° (decomp.) (Found : C, 55·9; H, 8·3; N, 10·8. $C_{12}H_{22}O_4N_2$ requires C, 55·8; H, 8·5; N, 10·8%), and 2 : 5-*diiso*butyl-1 : 4-*dihydroxy*-3 : 6-*dioxopiperazine* (from ethanol), needles, m. p. 253° (decomp.) (Found : C, 55·3; H, 8·6; N, 10·9%). All these gave red colours with methanolic ferric chloride and insoluble copper complexes with methanolic cupric acetate.

Reduction. 2 : 5-Di-n-butyl-1 : 4-dihydroxy-3 : 6-dioxopiperazine (0·1 g.) was heated under reflux with acetic acid (10 c.c.). Zinc dust (0·15 g.) was added during 1 hr. and the solution heated for a further 2 hr. On cooling and dilution with water, 2 : 5-di-n-butyl-3 : 6-dioxopiperazine (0·03 g.), m. p. 269°, separated.

3-n-*Butyl*-1 : 4-*dimethoxy*-2 : 5-*dioxopiperazine*.—3-n-Butyl-1 : 4-dihydroxy-2 : 5-dioxopiperazine (0·1 g.) was set aside overnight with excess of ethereal diazomethane, the solid dissolving. Evaporation gave the *ester* (0·11 g.) which crystallised from *cyclo*hexane as prisms, m. p. 98° (Found : 52·4; H, 8·0; N, 12·0; MeO, 21·9. $C_{10}H_{18}O_4N_2$ requires C, 52·2; H, 7·8; N, 12·2; 2MeO, 26·9%). 3-iso*Butyl*-1 : 4-*dimethoxy*-2 : 5-*dioxopiperazine*, m. p. 115° (Found : C, 52·6; H, 7·9; N, 12·2; MeO, 22·9%), was prepared similarly.

2 : 5-*Diisobutyl*-1 : 4-*dimethoxy*-3 : 6-*dioxopiperazine*.—2 : 5-Diisobutyl-1 : 4-dihydroxy-3 : 6-dioxopiperazine (0·05 g.) in ethanol (100 c.c.) was treated with excess of ethereal diazomethane. Evaporation of the solution and recrystallisation of the product from light petroleum (b. p.

60—80°) gave the *ether* as plates (0·02 g.), m. p. 130° (Found: C, 58·7; H, 9·1; N, 9·9. $C_{14}H_{26}O_4N_2$ requires C, 58·7; H, 9·1; N, 9·8%).

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798. *The Structure of Pulcherrimin.*

By A. H. COOK and C. A. SLATER.

New analytical and degradative evidence indicates that pulcherriminic acid [1,2] is to be formulated as 2 : 5-di*iso*butyl-3 : 4-dihydro-4 : 6-dihydroxy-3-oxopyrazine 1-oxide (VI). Consequently pulcherrimin, a natural pigment, is to be regarded as the corresponding ferric complex (V).

THE synthesis of 2 : 5-di*iso*butyl-1 : 4-dihydroxy-3 : 6-dioxopiperazine [2] (II) hitherto regarded as representing pulcherriminic acid [1] showed that the structure (I) of the iron pigment pulcherrimin, as postulated by Kluyver *et al.*,[3] must be incorrect and further degradative evidence was therefore sought.

Pulcherriminic acid, the parent metal-free compound, has now been found to yield a dimethyl ester, $C_{14}H_{24}O_4N_2$, which appears to contain two fewer hydrogen atoms than would be demanded on the original formulation. A reconsideration of all previous analyses in this connection shows that a molecular formula $C_{12}H_{20}O_4N_2$ is at least as acceptable as $C_{12}H_{22}O_4N_2$ suggested earlier [1] (see Table).

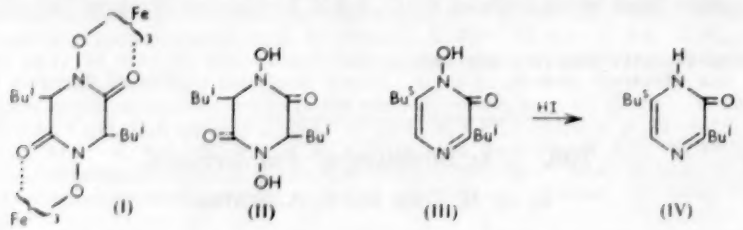
Compound	Formula	Required (%) C	H	N	Found (%) C	H	N
Pulcherriminic acid	$C_{12}H_{20}O_4N_2$	55·8	8·5	10·8	56·1	8·3	10·8
	$C_{12}H_{22}O_4N_2$	56·2	7·8	10·9			
Morpholine salt	$C_{20}H_{40}O_6N_4$	55·6	9·3	12·9	55·6	8·9	12·7
	$C_{20}H_{38}O_6N_4$	55·8	8·8	13·1			
*cyclo*Hexylamine salt	$C_{24}H_{48}O_4N_4$	63·2	10·5	12·3	63·3	10·2	12·4
	$C_{24}H_{44}O_4N_4$	63·5	10·1	12·3			

Comparison of the infrared absorption spectra of dimethyl pulcherriminate and aspergillic acid [4] (III), in the light of what is known of their chemistry, reveals that the main features of the two spectra show a remarkable similarity. Both compounds have strong bands at 2905 cm.$^{-1}$ around 1650 cm.$^{-1}$ [1675 cm.$^{-1}$ in aspergillic acid and 1645 cm.$^{-1}$ in dimethyl pulcherriminate (carbonyl stretching frequencies)], 1600, 1480, 1400 cm.$^{-1}$ (these three bands are all common to pyrazine), 1170, 820, 780, and 740 cm.$^{-1}$. The major differences consist in strong bands at 1258 and 1020 cm.$^{-1}$ in the spectrum of dimethyl pulcherriminate which are either absent from, or much weaker in, the spectrum of aspergillic acid. These bands are typical of aromatic ethers and point to the presence of a =C–O– grouping in dimethyl pulcherriminate. It is concluded, therefore, that aspergillic acid and dimethyl pulcherriminate possess several major structural features in common and, in particular, that dimethyl pulcherriminate possesses essentially a pyrazine rather than a piperazine nucleus.

When pulcherriminic acid was reduced with red phosphorus and iodine (cf. Dutcher [5]), a new compound, dideoxypulcherriminic acid, $C_{12}H_{20}O_2N_2$, was formed. This reaction is obviously comparable with the production of deoxyaspergillic acid (IV) from the antibiotic (III) itself. The new compound must, when account is taken of previous structural

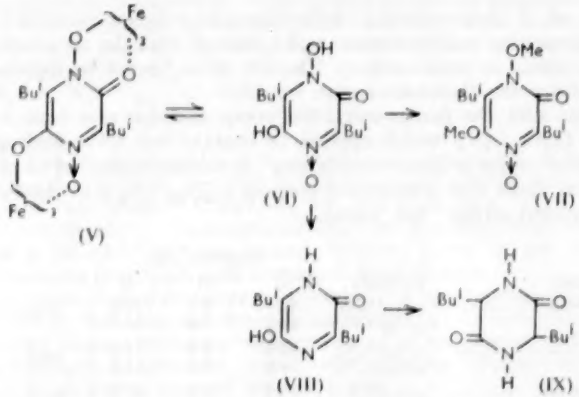
[1] Cook and Slater, *J. Inst. Brewing*, 1954, **60**, 213.
[2] Cook and Slater, preceding paper.
[3] Kluyver, van Triet, and van der Walt, *Proc. Nat. Acad. Sci. U.S.A.*, 1953, **39**, 583.
[4] Gore and Petersen, *Ann. N.Y. Acad. Sci.*, 1949, **51**, 924.
[5] Dutcher, *J. Biol. Chem.*, 1947, **171**, 321.

evidence regarding pulcherrimin, be formulated as (VIII), for only on further (catalytic) reduction is it converted into leucine anhydride (IX) which would almost inevitably be the



(I) (II) (III) (IV)

direct (phosphorus-iodine) reduction product of (II), the previous formulation for pulcherriminic acid. The infrared absorption spectrum of compound (VIII) is consistent with this structure.



(V) (VI) (VII) (VIII) (IX)

All these facts are accommodated by structure (VI) for pulcherriminic acid, the corresponding ester being (VII) and pulcherrimin itself (V).

Experimental

Dimethyl Pulcherriminate.—Pulcherriminic acid (1 g.) was treated with a small excess of ethereal diazomethane. Evaporation of the solution followed by distillation yielded a syrup (0·7 g.), b. p. 110—120°/10 mm., which crystallised. Recrystallisation from light petroleum gave the *dimethyl ester*, m. p. 81° [Found: C, 59·0, 58·9; H, 8·6, 8·5; N, 9·7, 9·6; MeO, 21·3, 21·8%; *M* (Rast), 250. $C_{14}H_{24}O_4N_2$ requires C, 59·2; H, 8·5; N, 9·7; 2MeO, 21·8%; *M*, 284]. Light absorption: in EtOH, $\lambda_{max.}$ 233, 289, 354 mμ (ε 24,400, 6250, 7350). This compound exhibits maximal absorption at the following wavelengths in the infrared region: 3·02w, 3·44s, 4·32w, 6·08s, 6·25s, 6·58w, 6·75s, 7·14s, 7·33s, 7·51m, 7·95s, 8·37m, 8·60m, 8·74m, 9·11m, 9·20w, 9·80s, 10·21s, 10·48w, 10·82w, 10·95m, 11·10s, 12·16m, 13·29m, 13·81m, and 14·65w μ, where s = strong, m = medium, w = weak.

Dideoxypulcherriminic Acid.—A solution of pulcherriminic acid (0·5 g.) in acetic acid (20 c.c.) was added to red phosphorus (0·3 g.), iodine (0·1 g.), and acetic acid (10 c.c.) in a 50-c.c. round-bottomed flask. After being heated under reflux for 3 hr., the hot solution was filtered into cold water (80 c.c.) containing sodium metabisulphite (1 g.). Recrystallisation of the flocculent, flesh-coloured precipitate from methanol gave *dideoxypulcherriminic acid* (0·24 g., 55%), decomp. 315°, fine needles [Found: C, 64·3, 64·3; H, 8·7, 8·5; N, 12·2, 12·4%; *M* (Rast), 233. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 8·9; N, 12·5%; *M*, 224]. Light absorption: in EtOH, $\lambda_{max.}$ 278 mμ (ε 13,250). Infrared maxima: 3·13s, 3·32s, 3·37s, 3·42s, 3·48m, 5·95s, 6·10s, 6·58w, 6·75s, 7·14s, 7·32s, 7·69m, 7·81m, 7·91w, 8·36w, 8·72m, 9·10w, 9·30w, 10·17w, 10·41w, 10·81s,

11·22w, 12·50s, and 13·31s μ. It gives no colour with ferric chloride solution, does not give a 2 : 4-dinitrophenylhydrazone, is insoluble in aqueous sodium hydrogen carbonate, and does not react with ethereal diazomethane.

Hydrogenation. A solution of dideoxypulcherriminic acid (0·025 g.) in methanol (50 c.c.) with Adams platinum catalyst (0·05 g.) was shaken with hydrogen for 3 hr. After filtration and evaporation to 5 c.c. small needles (0·015 g.) separated, having m. p. 269° alone or on admixture with authentic 2 : 5-di*iso*butyl-3 : 6-dioxopiperazine (m. p. 269°).

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799. *Heterocyclic Imines and Amines. Part VII.* N-Substituted Phthalic Imidine Derivatives and their Reactions with Amines.†*

By P. F. Clark, J. A. Elvidge, and J. H. Golden.

The condensation reactions of some *N*-substituted derivatives of di-imino-*iso*indoline with amines have been examined. In some cases there is direct replacement of the exocyclic imino-functions by the amine (as shown in *a*, below) but in other cases rearrangements are encountered (of the type *b*).

Structures have been determined, and light absorptions are given and discussed.

N-Methyl and other derivatives (I) of the imidine of phthalic acid have been prepared, and a preliminary examination has been made of their condensation reactions with primary amines. Two types of reaction have been encountered. In some cases there is a direct replacement of one or both of the exocyclic substituents, as indicated in the abbreviated reaction schemes *a* (i) and (ii). In other cases there is a rearrangement consequent upon the interaction, as indicated in *b* (i). Condensation with rearrangement has also been encountered with unsubstituted imidines : the overall reaction is then as in *b* (ii).

Three routes were used for the preparation of the imidine derivatives (I), *viz.*, condensation of amines with di-imino*iso*indoline,[1] alkylation of the imidine or its derivatives,[2] and the addition of amines to phthalonitrile.[2,3] For some of the required compounds, only one of the routes succeeded.

The structures of the new compounds were determined by mild hydrolysis with hydrochloric acid, a method which has proved reliable hitherto.[2,3,4] Compounds of the types (I; R′ = H) ‡ yield phthalimide whilst a compound of the type (I*A*; R′ ≠ H) yields an *N*-substituted phthalimide.

Preparations.—Di-imino*iso*indoline (I; R = R′ = R″ = H) with methyl iodide at 80° gave a lemon-yellow salt, $C_9H_{10}N_3I$. This was evidently the hydriodide of the 3-methyl derivative (I; R = Me, R′ = R″ = H) because hydrolysis yielded phthalimide and not *N*-methylphthalimide. From di-imino*iso*indoline and from phthalonitrile, with methylamine at 100°, 1 : 3-dimethylimino*iso*indoline (I; R = R″ = Me, R′ = H) was obtained : this base had one active hydrogen atom, gave a picrate and a hydrochloride, and on hydrolysis afforded phthalimide *via* the 3-methylimino-1-oxo-derivative (II; R = Me,

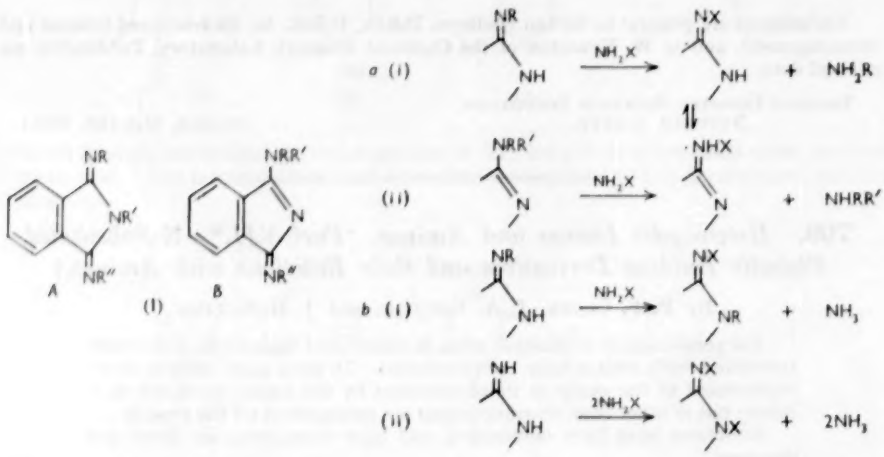
* Part VI, *J.*, 1956, 235.

† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

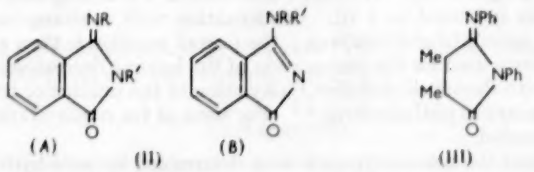
‡ The omission of *A* and *B* in the formula designation indicates that the compound is potentially tautomeric.

[1] Elvidge and Linstead, *J.*, 1952, 5000.
[2] Clark, Elvidge, and Linstead, *J.*, 1953, 3593.
[3] Elvidge and Linstead, *J.*, 1954, 442.
[4] Linstead and Whalley, *J.*, 1955, 3530.

R′ = H) which was isolated as the sparingly soluble hydrochloride. More vigorous treatment of di-imino*iso*indoline or 1 : 3-dimethylimino*iso*indoline with methylamine did not effect further methylation but gave a β-*iso*indigo compound.[5] However, a trimethyl derivative was obtained, as its yellow hydriodide, $C_{11}H_{14}N_2I$, from 1 : 3-dimethylimino*iso*indoline and methyl iodide at 100°. The trimethyl derivative yielded phthalimide on hydrolysis, which indicated the structure (I*B*; R = R′ = R″ = Me).



In parallel experiments, the imino-imide (II; R = R′ = H) was found to condense with 2 mols. of methylamine, rather than 1 mol. as expected from previous work.[1] The product, which gave *N*-methylphthalimide on hydrolysis, was necessarily the 2-methyl-3-methylimino-compound (II*A*; R = R′ = Me). Its formation was reminiscent of the



production of the derivative (III) from dimethylsuccinimidine and aniline hydrochloride.[4] Both reactions are examples of the type *b* (ii) condensation which must involve a rearrangement. With ethanolic solutions of *m*-aminoacetanilide and of piperidine, the imino-imide (II; R = R′ = H) yielded the "normal" derivatives (II; R = *m*-C_6H_4·NHAc, R′ = H) and (II*B*; RR′ = ·$[CH_2]_5$·), each of which gave phthalimide on hydrolysis. With aqueous-ethanolic ethylamine, however, there was hydrolysis of the imino-imide ring and formation of *NN′*-diethylphthalamide.

Attempts to obtain the unsymmetrical dimethyl derivative (I*B*; R = R′ = Me, R″ = H) by condensation of di-imino*iso*indoline with dimethylamine, or by addition of dimethylamine to phthalonitrile, failed. The only tractable product was phthalocyanine, which suggested that the required derivative was highly reactive. However, diethylamine was successfully added to phthalonitrile, and the very labile product, presumed to be the base (I*B*; R = R′ = Et, R″ = H), was isolated as the picrate. A similar labile base was obtained from morpholine and phthalonitrile. This was isolated as the hemihydrate and

[5] Elvidge and Golden, following paper.

characterised as the picrate. That the base had the cyclic structure (*IB*; RR′ = ·$[CH_2]_2$·O·$[CH_2]_2$·, R″ = H) was indicated by its hydrolysis with cold water to iminophthalimide (II; R = R′ = H) in good yield, a result which also demonstrated that the substituted amino-function was the more reactive of the two exocyclic nitrogen groups. Further work on compounds of this type is in progress.

The symmetrical 1 : 3-diethyl derivative (I; R = R″ = Et, R′ = H), which yielded phthalimide on hydrolysis, was obtained by the addition of ethylamine to phthalonitrile. 1 : 3-Dibenzyliminoisoindoline (I; R = R″ = CH_2Ph, R′ = H) was obtained by the alternative method, condensation of benzylamine in ethanol with di-iminoisoindoline: the product gave phthalimide on hydrolysis, as expected. Similarly prepared was 1 : 3-di-*m*-acetamidophenyliminoisoindoline, which crystallised as a stable hemihydrate. This disubstitution product was accompanied by a small quantity of the monosubstituted imidine, 3-*m*-acetamidophenylimino-1-iminoisoindoline (I; R = *m*-C_6H_4·NHAc, R′ = R″ = H), further reaction of which with *m*-aminoacetanilide gave the dicondensation product. Hydrolyses confirmed the structures.

Condensations.—The foregoing morpholino- and diethylamino-imines (*IB*; R″ = H, RR′ = ·$[CH_2]_2$·O·$[CH_2]_2$· and Et_2) soon became red or greenish-blue at ordinary temperature. Above 100°, alone or in solution, they rapidly decomposed with formation of phthalocyanine. This contrasted with the stability of di-iminoisoindoline itself, which gave phthalocyanine in appreciable yields only at elevated temperature in the presence of hydrogen donors.[6] For comparison, portions of the morpholino-imine were heated in boiling tetralin and in nitrobenzene: 33% yields of phthalocyanine were obtained within a few minutes, irrespective of whether the solvent was a hydrogen donor or dehydrogenating agent (cf. ref. 6).

With aniline in the cold, the morpholino- and the diethylamino-imine afforded the known monophenylimidine [2] (I; R = Ph, R′ = R″ = H) by a ready replacement of the substituted amino-group, and there was no production of ammonia. Treatment of the imines (*IB*; R″ = H, RR′ = ·$[CH_2]_2$·O·$[CH_2]_2$· and Et_2) with boiling butylamine rapidly afforded 1 : 3-dibutyliminoisoindoline [2] (I; R = R″ = Bu, R′ = H), both substituted and unsubstituted exocyclic nitrogen functions being replaced: in this reaction, therefore, ammonia was evolved. In extension, it was shown that 3-morpholino-1-oxoisoindolenine [2] (*IIB*; RR′ = ·$[CH_2]_2$·O·$[CH_2]_2$·) with aniline in boiling ethanol gave the phenyl analogue (II; R = Ph, R′ = H), that the monophenyl-imidine (I; R = Ph, R′ = R″ = H) with an excess of boiling butylamine yielded 1 : 3-dibutyliminoisoindoline (I; R = R″ = Bu, R′ = H), and that 1 : 3-dimethyliminoisoindoline with 2-aminopyridine yielded the 1 : 3-dipyridyl-imidine [1] (IV) with evolution of methylamine. These several reactions are examples of the type *a* direct-displacement condensations.

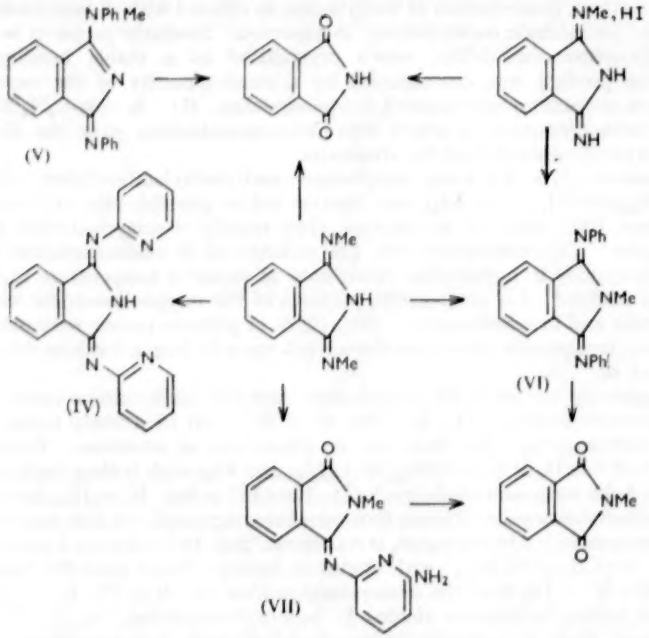
However, when 1 : 3-dimethyliminoisoindoline was heated with aniline (in contrast to aminopyridine) an unexpected reaction occurred. The product was, not the diphenyl-substituted imidine (I; R = R″ = Ph, R′ = H), but a methyl derivative which was isomeric with the known methyl derivative [2] (V). Hence the product evidently had the symmetrical 2-methyl-1 : 3-diphenylimino-structure (VI), and this was confirmed by its hydrolysis to *N*-methylphthalimide and 2 mols. of aniline. This condensation is thus accompanied by rearrangement and is of the type *b* (i). Similarly, the hydriodide of the monomethyl-imidine (I; R = Me, R′ = R″ = H) underwent rearrangement with aniline, to yield 2-methyl-1 : 3-diphenyliminoisoindoline (VI). A further example was the interaction of 1 : 3-dimethyliminoisoindoline and 2 : 6-diaminopyridine, which gave 3-(2-amino-6-pyridylimino)-2-methyl-1-oxoisoindoline (VII). A slight complication here was the incidental hydrolysis of one of the exocyclic nitrogen functions. The structure of the product was confirmed by its ready hydrolysis to *N*-methylphthalimide and 1 mol. of 2 : 6-diaminopyridine.

The yields of products from the various reactions were only 30—50%. We failed in each case to find other products, but obviously it remains uncertain that the reactions occur solely in the senses indicated. Indeed it appears, in general, that more than one reaction

[6] Elvidge and Linstead, *J.*, 1955, 3536.

course is open for any particular imidine–amine condensation. Further work on this topic is in hand.

Light Absorption and Fine Structure.—The ultraviolet light absorptions of the new imidine derivatives are given in the Table. Previous tentative generalisations [2,7] concerning the bond structures of imidines and their light absorptions are broadly confirmed. The conclusions are valid, of course, only if the various compounds compared have similar excited states. This seems probable within the limited field of phthalic imidine derivatives.



In the imino-imide series (II), the fully *N*-substituted (*i.e.*, fixed) *iso*indolines (II*A*) (see Table) have a maximum in the region of 3000 Å, irrespective of whether the substituents are alkyl, aryl, or heteroaryl. There is very little doubt therefore that the potentially tautomeric parent imino-imide [2] (II; R = R′ = H), its monomethyl derivative, their hydrochlorides, and the oxime [3] (II; R = OH, R′ = H) all exist in the bond form (II*A*). (It is presumably the exocyclic imino-group which is protonated in the salts.) The fixed alkyl-substituted *iso*indolenine (II*B*; RR′ = ·$[CH_2]_5$·), like the related morpholino-derivative,[2] has a maximum in the region of 3400 Å. The incompletely substituted *N*-aryl and *N*-heteroaryl derivatives (II; R′ = H) have maxima in the region of 3380—3830 Å.[1,2] The conclusion [2] that these exist in the form (II*B*) is fully justified: the only exception is the 3-pyridyl derivative (II; R = 3-C_5H_4N, R′ = H) which may be a tautomeric mixture of the forms *A* and *B* in solution. The variations in the position of the band of longest wavelength for the compounds (II*B*; R′ = H) indicate that *N*-substituents in the *iso*indolenine structure have appreciable auxochromic effects. This contrasts with the absence of substituent effects in the true *iso*indolines (II*A*).

In the di-imino*iso*indoline series (I) similar considerations appear to apply.

In this series we have prepared for the first time a compound with the fixed structure (I*A*), *viz.*, the derivative (VI). This shows a maximum at 3050 Å. In contrast, the isomer (V) and related *iso*indolenines [2] have maxima at 3680—3790 Å. Of particular

[7] Clark, Elvidge, and Linstead, *J.*, 1954, 2490.

interest also is the alkyl-substituted *iso*indolenine (I*B*; R = R′ = R″ = Me) which was obtained in methanol solution from the hydriodide and 1 equivalent of sodium methoxide: the base shows an absorption maximum at 3480 Å.

Light absorptions in methanol and water.

Compound	$\lambda_{max.}$ (Å)	ε	Compound	$\lambda_{max.}$ (Å)	ε
(VI)	2270	26,400	(I; R = R″ = Et, R′ = H)	2650	11,100
	2580	19,900		3120	3,800
	2650				
	3050	9,600	(I; R = R″ = CH_2Ph, R′ = H)	2650	15,000
				3160	4,700
(V) [2]	2580	11,200			
	2680	12,400	(II*A*; R = R′ = Me)	2500	14,300
	2810			2980	3,500
	2900				
	3680	14,600	(II*A*; R = Ph, R′ = Me) [3]	2510	18,900
				2810	3,800
(I*B*; R = R′ = R″ = Me)	2790	12,200		2910	
	3480	3,900		3020	
,, ,HI	2270	31,500	(II*A*; R = 2-NH_2-6-pyridyl, R′ = Me)	2430	18,900
	2800	12,900		3030	7,000
	3180 †	5,000			
	3540	3,800	(II; R = R′ = H),HCl [1]	* 2260	26,000
(I; R = R″ = Me, R′ = H)	2520	11,100		2980	1,000
	2660	14,000			
	3080	7,300	(II; R = Me, R′ = H),HCl	* 2480	16,100
				3060	3,900
,, ,, ,HCl	2725	17,000			
	3070	6,100	(II*B*; RR′ = $[CH_2]_4$)	2620	10,000
	3350	3,900		3070	1,500
				3380	

* In H_2O; others in MeOH. † Inflexion.

The new results strongly suggest that the potentially tautomeric parent imidine (I; R = R′ = R″ = H), the dioxime [3] (I; R = R″ = OH, R′ = H), and the dimethyl derivative, which have maxima in the region of 3000 Å, exist entirely in the di-imino*iso*indoline form (I*A*). The other dialkyl derivatives (I) listed in the Table show maxima at slightly longer wavelengths, like the dibutyl compound [2] (I; R = R″ = Bu, R′ = H), so it appears that these tautomerise a little to the form (I*B*) in solution. In the *N*-aryl and *N*-heteroaryl derivatives [2] (I; R′ = H) the tautomeric form (I*B*) must predominate because these compounds all show absorption maxima above 3500 Å. It now seems that the individual variations in position of the longest-wavelength band are substituent effects, which appear in aminoimino*iso*indolenines (I*B*) but not in di-imino*iso*indolines (I*A*).

Experimental

Analyses were performed in the microanalytical laboratories (Mr. F. H. Oliver) and light absorption measurements were made in the spectrographic laboratory (Mrs. A. I. Boston) of this Department.

Monomethyl Derivative of Di-iminoisoindoline.—The imidine [1] (I; R = R′ = R″ = H) (1 g.) was heated with methyl iodide (5 c.c.) at 80° for 18 hr. Recrystallisation of the substantially pure product (1·83 g., 100%) from dry methanol afforded yellow needles of *1-imino-3-methyliminoisoindoline hydriodide*, m. p. 250° (decomp.) (Found: C, 37·6; H, 4·0; N, 14·4. $C_9H_{10}N_3I$ requires C, 37·7; H, 3·5; N, 14·6%).

When this salt (414 mg.) was boiled with 2N-hydrochloric acid (5 c.c.) for 2 min. the yellow colour was discharged. The solution was then kept at 0° overnight. Phthalimide separated (132 mg., 0·63 mol.), having m. p. and mixed m. p. 232°.

1 : 3-Dimethyliminoisoindoline (I; R = R″ = Me, R′ = H).—(a) *Preparation.* (i) A mixture of di-imino*iso*indoline (5 g.), dry ethanol (20 c.c.), and liquid methylamine (10 c.c.) was heated at 100° for 16 hr. The orange solution was evaporated to dryness under reduced pressure, the residue was dissolved in benzene, and the solution treated with charcoal. Concentration and

cooling of the solution afforded **1 : 3-*dimethyliminoisoindoline*** (3·3 g., 56%), m. p. 168—169°, which crystallised from ethyl acetate as colourless needles, m. p. 172° (decomp.) [Found : C, 69·2; H, 6·7; active H ($LiAlH_4$ in Bu_2O), 0·57; N, 24·7. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; 1 active H, 0·58; N, 24·3%].

(ii) Phthalonitrile (5 g.), dry ethanol (20 c.c.), and liquid methylamine (10 c.c.) were heated at 100° for 24 hr. Treatment of the solution as in (i) yielded **1 : 3-**dimethyliminoisoindoline (5·3 g., 78%) with m. p. 164—165° (decomp.), raised to 172° (decomp.) on recrystallisation from ethyl acetate.

The *picrate*, prepared in methanol and extractively crystallised from ethanol, formed yellow prisms, m. p. 264° (decomp.) (Found : C, 47·8; H, 3·7; N, 20·6. $C_{15}H_{12}O_7N_6$ requires C, 47·8; H, 3·5; N, 20·9%).

Treatment of the base in ethanol with ethereal hydrogen chloride, and crystallisation of the precipitate from water at 0° by addition of dioxan, afforded minute needles of the ***hydrochloride***, m. p. 296° (decomp.) (Found : C, 57·1; H, 5·7; Cl, 16·8. $C_{10}H_{12}N_3Cl$ requires C, 57·3; H, 5·8; Cl, 16·9%).

(b) *Hydrolysis.* The base (282 mg.) with warm 2N-hydrochloric acid (3 c.c.) gave needles of a hydrochloride, but boiling the mixture for 5 min. afforded a clear solution. At 0° overnight, this deposited phthalimide (150 mg., 0·63 mol.), m. p. and mixed m. p. 234°. The intermediate ***3-methylimino-1-oxoisoindoline hydrochloride*** (II; R = Me, R′ = H),HCl crystallised as needles, m. p. 319° (decomp.), from water on addition of ethanol (Found : C, 54·9; H, 4·7. $C_9H_9ON_2Cl$ requires C, 54·95; H, 4·6%).

Trimethyl Derivative of Di-iminoisoindoline.—**1 : 3-**Dimethyliminoisoindoline (1 g.) was heated with an excess of methyl iodide at 100° for 15 hr., and the solid product (1·64 g.), m. p. 260° (decomp.), was recrystallised five times from a **1 : 3** mixture of benzyl alcohol and ethanol : the ***3-dimethylamino-1-methyliminoisoindolenine hydriodide*** (*IB*; R = R′ = R″ = Me),HI separated as yellow prisms (0·22 g.), m. p. 269—270° (decomp.) (Found : C, 41·7; H, 4·7; N, 12·9. $C_{11}H_{14}N_3I$ requires C, 41·9; H, 4·5; N, 13·3%). The salt (26·6 mg.) was boiled with 2N-hydrochloric acid (2 c.c.) for 2 min. and the solution was then kept overnight at room temperature. Phthalimide (4·8 mg., 0·39 mol.), m. p. and mixed m. p. 231°, separated.

Action of Methylamine on 3-Imino-1-oxoisoindoline (II; R = R′ = H).—This imino-imide [1] (4·5 g.), ethanol (15 c.c.), and liquid methylamine (10 c.c.) were heated together at 100° for 18 hr. The solution was treated with charcoal and was then concentrated, whereupon a white solid separated (3·8 g., 71%), having m. p. 136°. From methanol, ***2-methyl-3-methylimino-1-oxoisoindoline*** (*IIA*; R = R′ = Me) formed needles, m. p. 138·5° (Found : C, 69·2; H, 6·0; N, 16·4. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8; N, 16·1%).

Boiling the compound (72 mg.) with 2N-hydrochloric acid (2 c.c.) for 2 min. and cooling the solution at 0° overnight afforded *N*-methylphthalimide (59 mg., 0·89 mol.), m. p. and mixed m. p. 135°.

3-m-Acetamidophenylimino-1-oxoisoindoline (II; R = *m*-C_6H_4·NHAc, R′ = H).—*m*-Aminoacetanilide [2] (1 g.) and 3-imino-1-oxoisoindoline (1 g.) were boiled in ethanol (20 c.c.) for 17 hr. From ethanol, ***3-m-acetamidophenylimino-1-oxoisoindoline*** (1·18 g., 61%) formed pale yellow needles, m. p. 245—246° (Found : C, 68·7; H, 4·8; N, 15·4. $C_{16}H_{15}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·0%).

A suspension of the compound (500 mg.) in 2N-hydrochloric acid (20 c.c.) was stirred and heated on the steam-bath for 5 min. The mixture was then cooled and the mass of needles of phthalimide collected (228 mg., 0·86 mol.); they had m. p. 230—231° and mixed m. p. 231—232°. The filtrate was evaporated to dryness under reduced pressure, and the residue heated in pyridine (10 c.c.) with toluene-*p*-sulphonyl chloride (0·4 g.) for 30 min. on the steam-bath. The excess of pyridine was removed under reduced pressure, and the oily residue taken up in 2N-sodium hydroxide. The solution was filtered, cooled, and acidified, and the crystalline precipitate then triturated with aqueous sodium hydrogen carbonate. From aqueous ethanol, *NN′*-ditoluene-*p*-sulphonyl-*m*-phenylenediamine (223 mg., 0·31 mol.) crystallised as laths, m. p. and mixed m. p. 171—172°.

The ***toluene-p-sulphonyl derivative*** of *m*-aminoacetanilide formed parallelogrammic plates (from ethanol–water), m. p. 182° (Found : C, 59·05; H, 5·4; N, 9·4. $C_{15}H_{16}O_3N_2S$ requires C, 59·2; H, 5·3; N, 9·2%), and depressed the m. p. of the previous derivative to 149—160°.

1-Oxo-3-piperidinoisoindolenine.—3-Imino-1-oxoisoindoline (2 g.), piperidine (3 c.c., redistilled), and ethanol (25 c.c.) were boiled together for 20 hr. The solution was treated with

[1] Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 1447.

charcoal and concentrated under reduced pressure, and the residue was triturated with light petroleum (b. p. 60—80°) and then dissolved in benzene (10 c.c.). When cooled, the solution deposited 1-*oxo*-3-*piperidinoisoindolenine* (2·3 g., 78%), m. p. 137—140°, which on recrystallisation from ethyl acetate gave creamy-yellow prisms, m. p. 143° (Found: C, 73·1; H, 6·7; N, 13·7. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·6; N, 13·1%).

Action of Aqueous Ethylamine on 3-*Imino*-1-*oxoisoindoline.*—A solution of the imino-imide (1·45 g.) in ethanol (40 c.c.) and 30% aqueous ethylamine (1·5 c.c.) was heated on the steam-bath for 3 hr., and then evaporated. The residue was triturated with ether, and the solid extracted with benzene. Recrystallisation of the extract from benzene yielded *NN'*-diethylphthalamide, m. p. and mixed m. p. 161—162°.

1-*Imino*-3-*morpholinoisoindolenine* (1*B*; RR' = ·$[CH_2]_2$·O·$[CH_2]_2$·, R'' = H).—Sodium (5 mg.) was treated with methanol (25 c.c.). Morpholine (1·74 g.) and phthalonitrile (2·56 g.) were added and the mixture was boiled for 3 hr. Traces of phthalocyanine (3·2 mg.) were removed and the filtrate was evaporated. The greenish crystalline residue (1·44 g.) was washed with acetone and dissolved in cold methanol, and, without delay, the solution was treated with charcoal and concentrated under reduced pressure, and the cream-coloured solid transferred to the filter with dioxan. Recrystallisation was effected by evaporating a methanol solution to very small bulk and then adding dioxan slowly: 1-*imino*-3-*morpholinoisoindolenine* separated as pale cream-coloured prisms (0·8 g.), which became progressively darker blue above 100° without melting, and had an instantaneous melting-decomposition point at 174° (Found, on different preparations, dried at room temperature: C, 64·7, 64·7, 63·8; H, 5·6, 6·15, 6·3; N, 18·9, 19·2. $C_{12}H_{13}ON_3,\frac{1}{2}H_2O$ requires C, 64·3; H, 6·3; N, 18·7%). To the base (100 mg.) in methanol (1 c.c.), picric acid (107 mg.) in methanol (2 c.c.) was added. The precipitated *picrate* (188 mg.) had m. p. 240° (decomp.) (rapid heating) (Found: N, 19·3. $C_{18}H_{16}O_8N_6$ requires N, 18·9%).

The base (614 mg.) slowly dissolved (18 hr.) in water (2 c.c.) at room temperature. The solution smelled of morpholine, and during 2 days deposited 3-imino-1-oxo*iso*indoline (344 mg., 0·80 mol.), m. p. and mixed m. p. 205°.[3]

3-*Diethylamino*-1-*imino*isoindolenine (1*B*; R = R' = Et, R'' = H).—Phthalonitrile (2·56 g.) and diethylamine (1·46 g.) were added to methanol (25 c.c.) with which sodium (5 mg.) had reacted, and the mixture was boiled for 3 hr. Traces of phthalocyanine were filtered off, the solution was evaporated under reduced pressure, the crystalline residue was dissolved in ether, and the solution was treated with charcoal and then evaporated to small bulk. 3-Diethylamino-1-imino*iso*indolenine separated as pale yellowish crystals (0·5 g.), m. p. 59°. The *picrate*, prepared in ethanol, was crystallised extractively from ethanol to yield yellow needles, m. p. 212° (decomp.) (Found: C, 50·7; H, 4·5; N, 19·5. $C_{18}H_{18}O_7N_6$ requires C, 50·2; H, 4·2; N, 19·5%).

1 : 3-*Diethyliminoisoindoline* (I; R = R'' = Et, R' = H).—A solution of phthalonitrile (5 g.) in ethanol (15 c.c.) containing dry ethylamine (10 c.c.) was heated at 100° for 36 hr. and then evaporated under reduced pressure. After 3 days at 0°, the residue crystallised: trituration with ether–light petroleum (b. p. 60—80°) afforded a cream-coloured solid (4·9 g., 63%), m. p. 154—155°. From ethyl acetate, the 1 : 3-*diethyliminoisoindoline* formed colourless prisms, m. p. 158° (Found: C, 71·2; H, 7·4; N, 21·0. $C_{12}H_{15}N_3$ requires C, 71·6; H, 7·5; N, 20·9%).

Hydrolysis of the base (500 mg.) with boiling 2N-hydrochloric acid (5 c.c.) for 5 min. and cooling of the solution (4 hr. at 0°) afforded phthalimide (326 mg., 0·89 mol.) as needles, m. p. and mixed m. p. 230°.

1 : 3-*Dibenzyliminoisoindoline* (I; R = R'' = CH_2Ph, R' = H).—Di-imino*iso*indoline (3 g.), ethanol (25 c.c.) and benzylamine (6 c.c.) were heated together under reflux for 24 hr. Ammonia was evolved. On evaporation of the solution under reduced pressure a semi-solid mass was obtained, which was drained on porous tile. Crystallisation of the solid (5·9 g.), m. p. 130—150°, from toluene provided 1 : 3-*dibenzyliminoisoindoline* (5·1 g., 76%) as cream-coloured rods, m. p. 160° (Found: C, 81·3; H, 6·0; N, 13·1. $C_{22}H_{19}N_3$ requires C, 81·2; H, 5·9; N, 12·9%).

The base (247 mg.) was boiled in ethanol (2 c.c.) and 50% aqueous hydrochloric acid (2 c.c.) for 30 min. Water (5 c.c.) was added and the solution was concentrated under reduced pressure and cooled to 0°. Phthalimide separated (98 mg., 0·88 mol.), having m. p. and mixed m. p. 232°.

1 : 3-*Di*-m-*acetamidophenyliminoisoindoline and* 3-m-*Acetamidophenylimino*-1-*iminoisoindoline.*—Di-imino*iso*indoline (0·5 g.) and *m*-aminoacetanilide[4] (1 g.) were boiled in ethanol (40 c.c.) overnight, and the mixture was then cooled. The 1 : 3-*di*-m-*acetamidophenyliminoisoindoline* (I; R = R'' = *m*-C_6H_4·NHAc, R' = H) (0·85 g.), m. p. 260°, was recrystallised from propylene carbonate to yield yellow prisms, m. p. 261° (decomp.), of a stable *hemihydrate* (Found,

in different preparations, dried at 140°/15 mm. for 2 hr.: C, 69·1, 68·2, 68·55; H, 5·3, 5·1, 5·2; N, 16·4, 16·55, 16·75. $C_{24}H_{21}O_2N_5,\frac{1}{2}H_2O$ requires C, 68·6; H, 5·3; N, 16·7%).

Evaporation of the filtrate from this product afforded 3-m-*acetamidophenylimino*-1-*imino*iso*indoline* (I; R = *m*-C_6H_4·NHAc, R′ = R″ = H) (0·3 g.), m. p. 239°, which crystallised from ethanol as pale, slightly greenish, yellow prismatic needles, m. p. 240—241° (Found: C, 68·8; H, 5·2; N, 20·3. $C_{16}H_{14}ON_4$ requires C, 69·05; H, 5·1; N, 20·1%). The m. p. was depressed to 228° by 3-*m*-acetamidophenylimino-1-oxo*iso*indoline (above).

The 3-*m*-acetamidophenylimino-1-imino*iso*indoline (300 mg.) was stirred with concentrated hydrochloric acid (6 c.c.) and heated on the steam-bath for 10 sec.[3] The suspension was at once diluted with water, chilled, and poured into an excess of aqueous ammonia. The pale yellow precipitate (124 mg.) had m. p. 239—240° and mixed m. p. 241—244° with 3-*m*-acetamidophenylimino-1-oxo*iso*indoline (above).

3-*m*-Acetamidophenylimino-1-imino*iso*indoline (0·5 g.) and *m*-aminoacetanilide (0·27 g.) were boiled together in 2-methoxyethanol (10 c.c.) overnight. Evaporation of the solution and trituration of the residue with ethanol afforded 1 : 3-di-*m*-acetamidophenylimino*iso*indoline hemihydrate (0·2 g.), m. p. and mixed m. p. 261° (decomp.).

1 : 3-Di-*m*-acetamidophenylimino*iso*indoline (340 mg.) was boiled with 2N-hydrochloric acid (20 c.c.) for 15 min., and undissolved solid (74 mg.) removed. Cooling the filtrate to 0° afforded needles of phthalimide (103 mg., 0·86 mol.), m. p. and mixed m. p. 230—231°.

Displacement Reactions.—(i) 1-Imino-3-morpholino*iso*indolenine (I*B*; RR′ = ·$[CH_2]_2$·O·$[CH_2]_2$·, R″ = H) (455 mg.) in methanol (5 c.c.) was kept with aniline (197 mg.) for 24 hr. Yellow crystals separated: a second crop, obtained by concentration of the mother-liquors under reduced pressure, was washed with a little acetone. The product (217 mg., 46%) had m. p. 199—203° (decomp.) undepressed by 1-imino-3-phenylimino*iso*indoline (I; R = Ph, R′ = R″ = H), m. p. 203° (decomp.).[3]

(ii) 3-Diethylamino-1-imino*iso*indolenine (I*B*; R = R′ = Et, R″ = H) (1 g.) in ethanol (10 c.c.) with aniline (460 mg.) for 24 hr. similarly gave 1-imino-3-phenylimino*iso*indoline (I; R = Ph, R′ = R″ = H) (387 mg., 35%), m. p. and mixed m. p. 202° (decomp.).

(iii) 1-Imino-3-morpholino*iso*indolenine (433 mg.) and butylamine (5 c.c.) were heated under reflux until the evolution of ammonia slackened. The butylamine was evaporated off, the residue taken up in ether, and the solution treated with charcoal. Concentration of the filtrate afforded needles of 1 : 3-dibutylimino*iso*indoline (I; R = R″ = Bu, R′ = H) (133 mg.), m. p. and mixed m. p. 132°.[3]

(iv) Similarly, 3-diethylamino-1-imino*iso*indolenine (1 g.) and boiling butylamine afforded 1 : 3-dibutylimino*iso*indoline (720 mg., 56%), m. p. and mixed m. p. 131—132°.

(v) 3-Morpholino-1-oxo*iso*indolenine[2] (II*B*; RR′ = ·$[CH_2]_2$·O·$[CH_2]_2$·) (500 mg.) in ethanol (10 c.c.) was heated under reflux with aniline (0·5 g.) for 17 hr. No ammonia was evolved. Evaporation of the solution to small bulk, and cooling, afforded 1-oxo-3-phenylimino*iso*indoline (II; R = Ph, R′ = H) (396 mg., 77%), m. p. and mixed m. p. 168—171°.[1]

(vi) 1-Imino-3-phenylimino*iso*indoline (I; R = Ph, R′ = R″ = H) (2 g.), butylamine (5 c.c.), and ethanol (10 c.c.) were boiled together for 18 hr. Ammonia was evolved. The solution was evaporated, the residue was taken up in ether, and light petroleum (b. p. 40—60°) added. Crystallisation of the precipitate from *cyclo*hexane (charcoal) gave yellow needles (1·14 g., 49%), m. p. 128—129°, of 1 : 3-dibutylimino*iso*indoline (I; R = R″ = Bu, R′ = H), which had m. p. and mixed m. p. 130° after a recrystallisation (Found: C, 75·1; H, 9·2; N, 16·9. Calc. for $C_{16}H_{13}N_3$: C, 74·7; H, 9·0; N, 16·3%).

(vii) 1 : 3-Dimethylimino*iso*indoline (2 g.) and 2-aminopyridine (4 g.) were boiled together in ethyl carbitol (diethylene glycol ethyl ether) (7·5 c.c.) for 11 hr. Methylamine was evolved. Evaporation under reduced pressure yielded a brown gum which was dissolved in benzene. The solution was treated with charcoal and then chromatographed on a column (12 × 3·5 cm.) of alumina (Brockmann grade II). The first, fast-moving yellow band was eluted with benzene (500 c.c.). Evaporation of the eluate afforded a yellow solid. Other brown bands on the column provided intractable oils. Rechromatography of the solid in benzene on a similar column, and elution with benzene (1250 c.c.) and 10% chloroform–benzene (750 c.c.) provided 1 : 3-di-2′-pyridylimino*iso*indoline[1] (IV) (162 + 330 mg.), m. p. and mixed m. p. 179—180° after recrystallisation from ethanol. Further elution of the column with 20% acetone–benzene (300 c.c.) yielded 2-aminopyridine (60 mg.), m. p. and mixed m. p. 54° after a recrystallisation from light petroleum (b. p. 40—60°).

Condensations with Rearrangement.—(i) 1 : 3-Dimethylimino*iso*indoline (596 mg.), aniline (2 c.c.), and ethyl carbitol (5 c.c.) were heated together under reflux. Methylamine was evolved,

After 5 hr., the solution was evaporated under reduced pressure, and the residual gum was triturated with light petroleum (b. p. 60—80°) and then dissolved in ethanol. The solution was treated with charcoal and evaporated, and the residue was taken up in benzene (15 c.c.) and chromatographed on a column (12 × 3·5 cm.) of alumina (Brockmann grade II). The eluate which contained the material of the slower-moving of the two yellow bands was rechromatographed similarly. Evaporation of the final eluate yielded *2-methyl-1 : 3-diphenyliminoisoindoline* (VI) (201 mg.) which crystallised from ethanol as lemon-yellow leaflets (66 mg.), m. p. 190—191° (Found : C, 81·1; H, 5·6; N, 13·8. $C_{21}H_{17}N_3$ requires C, 81·0; H, 5·5; N, 13·5%). No other solid product was isolated. Repetition of the condensation in boiling ethanol for 24 hr. gave 2-methyl-1 : 3-diphenyliminoisoindoline in much poorer yield.

1-Imino-3-methyliminoisoindoline hydriodide (1 g.) was boiled in ethanol (25 c.c.) with aniline (2·5 c.c.). Ammonia was evolved. After 12 hr., the solution was concentrated under reduced pressure to 15 c.c., and cooled. 2-Methyl-1 : 3-diphenyliminoisoindoline (VI) (0·32 g.) separated; its m. p. and mixed m. p. (190—191°) were unchanged on recrystallisation from aqueous ethanol (Found : C, 80·9; H, 5·5; N, 13·5%). Chromatography of the material of the mother-liquors, in benzene on alumina, as previously, provided a less pure second crop (0·25 g.), m. p. 175—180°.

2-Methyl-1 : 3-diphenyliminoisoindoline (VI) (53·4 mg.) in ethanol (1 c.c.) was warmed on the steam-bath with 2N-hydrochloric acid (2 c.c.) for 10 min. Cooling the solution caused the separation of colourless needles of *N*-methylphthalimide (21·2 mg., 0·77 mol.), m. p. and mixed m. p. 131°. Diazotisation of the filtrate and addition of aqueous alkaline β-naphthol yielded phenylazo-β-naphthol (70·5 mg., 1·77 mol.) as dark red needles, m. p. and mixed m. p. 129°.

(ii) 1 : 3-Dimethyliminoisoindoline (1·7 g.) and 2 : 6-diaminopyridine (3·4 g.) were boiled together in ethyl carbitol (10 c.c.) for 17 hr. Removal of the solvent under reduced pressure left a black tar which was taken up in acetone (100 c.c.). The solution was filtered, treated with charcoal, and evaporated. The residue was dissolved in 10% acetone-in-benzene (50 c.c.), and the solution was filtered and then chromatographed on a column (12 × 3·5 cm.) of alumina (Brockmann grade II). Development of the chromatogram with the same solvent afforded a brown, an orange and a (fastest) yellow band. Elution of the material of the yellow zone with the same solvent (1500 c.c.), evaporation of the eluate, and draining of the residue on porous tile gave a crude yellow powder (1·04 g.). Continuous extraction of this with light petroleum (b. p. 80—100°) for 36 hr. removed a little 2 : 6-diaminopyridine. Crystallisation of the residue from benzene (charcoal) and then from toluene provided *3-(2-amino-6-pyridylimino)-2-methyl-1-oxoisoindoline* (VII) as orange-yellow needles, m. p. 198° (decomp.) [Found : C, 66·2; H, 4·8; N, 22·0%; *M* (Rast), 253. $C_{14}H_{12}ON_4$ requires C, 66·7; H, 4·8; N, 22·2%; *M*, 252]. From the middle zone of the column, a trace of red gum was eluted. From the top brown band, 10% ethanol-in-benzene (900 c.c.) eluted a reddish tar (1·3 g.) from which boiling ligroin (b. p. 100—120°) extracted 2 : 6-diaminopyridine (0·4 g.), m. p. and mixed m. p. 120°.

3-(2-Amino-6-pyridylimino)-2-methyl-1-oxoisoindoline (44 mg.) was warmed on the steam-bath with 2N-hydrochloric acid (1 c.c.) for 20 min., by which time the colour was discharged. After 2 hr. at 0°, needles of *N*-methylphthalimide (21·6 mg., 0·77 mol.) had separated (m. p. 130° and mixed m. p. 132°). Treatment of the filtrate with a saturated solution of picric acid in ethanol (1 c.c.) caused precipitation of 2 : 6-diaminopyridine picrate (36 mg., 0·61 mol.), m. p. and mixed m. p. 236°.

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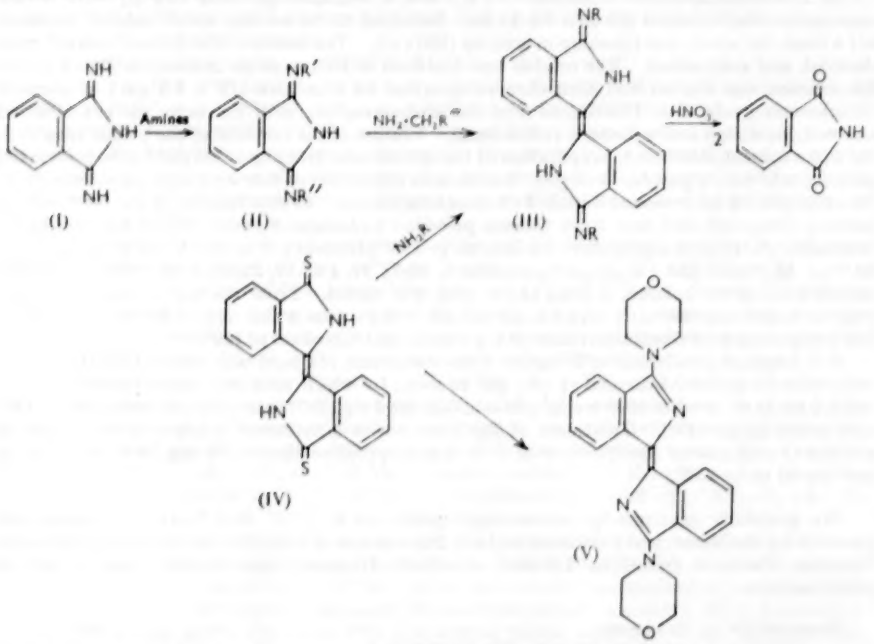
800. *Compounds containing Directly Linked Pyrrole Rings. Part II.* Dialkylimino-β-isoindigos.*

By J. A. Elvidge and J. H. Golden.

1 : 3-Dimethyliminoisoindoline (II; R′ = R″ = Me) with methylamine at 200° affords dimethylimino-β-*iso*indigo † [di-(3-methylimino-1-*iso*indolinylidene)] (III; R = Me), which on oxidative hydrolysis gives 2 mols. of phthalimide. Dibutyl- and dibenzyl-imino-β-*iso*indigo (III; R = Bu and CH_2Ph) are obtained analogously: they can also be prepared from dithio-β-*iso*indigo (IV) with butylamine and benzylamine respectively. Condensation of morpholine with dithio-β-*iso*indigo gives a derivative with the fixed-bond structure (V). Light absorptions are given, and the fine structure of the new β-*iso*indigo derivatives is discussed.

Their formation from imidines and alkylamines evidently proceeds *via* a bimolecular reduction, the alkylamine, $R'''\cdot CH_2\cdot NH_2$, acting as the hydrogen donor.

Treatment of di-imino*iso*indoline (I) with primary amines under mild conditions yields substituted imino*iso*indolines (II).[1,2,3] We now find that under more vigorous conditions, β-*iso*indigo derivatives (III) are formed. This unexpected reaction (II) ⟶ (III) is a bimolecular reduction.



Di-imino*iso*indoline (I) or phthalonitrile with methylamine at 100° gave 1 : 3-dimethyliminoisoindoline [3] (II; R′ = R″ = Me). When this compound, $C_{10}H_{11}N_3$, was heated with methylamine at 200°, in an attempt to prepare a trimethyl derivative, a high-melting

* Part I, *J.*, 1956, 244.

† Drew and Kelly (*J.*, 1941, 625, 630) called the compound (IV) "dithio-β-*iso*indigo."

[1] Elvidge and Linstead, *J.*, 1952, 5000.

[2] Clark, Elvidge, and Linstead, *J.*, 1953, 3593.

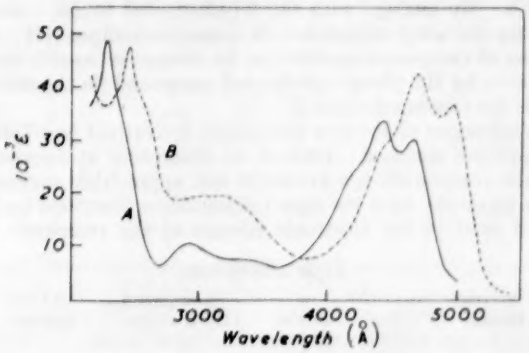
[3] Clark, Elvidge, and Golden, preceding paper.

orange product was obtained instead, whose analyses indicated a formula $C_9H_8N_2$. This was got in better yield from phthalonitrile and methylamine without the isolation of intermediate imidines.

The new product gave values for active hydrogen of approximately 0·5 and 1, by the Zerewitinoff and the lithium aluminium hydride method, respectively. The compound was practically unaffected by boiling dilute sodium hydroxide, hydrochloric acid, or sulphuric acid. However, boiling dilute nitric acid readily effected oxidative hydrolysis to phthalimide (in high yield) and methylamine, a result which indicated the presence of the intact *iso*indoline nucleus. The fragments $C_6H_4\langle{}^{C}_{C}\rangle NH$ and NMe accounted for the empirical formula but could not provide a feasible structure or account for 0·5 atom of active hydrogen. Hence it was concluded that the orange compound must have a " double " molecule, $C_{18}H_{16}N_4$, *i.e.*, that it had the β-*iso*indigoid structure (III; R = Me). Support for this came first from a molecular-weight determination in acetone by a modification of the Barger method.[4]

Proof of the structure (III; R = Me) was achieved by a synthesis from dithio-β-*iso*indigo (IV) and ethanolic methylamine. Drew and Kelly [5] had earlier prepared the

Light absorption of (A) di-(3-methylimino-1-isoindolinylidene) (in dioxan) and (B) di-(3-phenylimino-1-isoindolinylidene) (in ethanol).



diphenylimine (III; R = Ph) by this route. The light absorptions of these imines are similar (see Figure).

Benzylamine and butylamine behaved similarly to methylamine when reacting with imidines at elevated temperatures. Thus heating 1 : 3-dibenzylimino*iso*indoline (II; R′ = R″ = CH_2Ph) with benzylamine in butanol, or di-imino*iso*indoline (I) with butylamine at 200°, afforded orange products, $C_8H_5N_2R$, where R = C_7H_7 or C_4H_9, respectively.

These had similar general properties and light absorptions (see Table) to the methylamine product and were presumably the β-*iso*indigoid imines (III). Oxidative hydrolyses did not proceed cleanly, however, although the dibenzylimine gave some phthalimide, together with benzaldehyde, presumably from oxidation of the benzylimino-groups. Attempted conversion of the imines (III) into dithio-β-*iso*indigo (IV) failed. The structures (III; R = CH_2Ph and C_4H_9) were made certain, however, by the syntheses (IV) ⟶ (III), from dithio-β-*iso*indigo with benzylamine and butylamine. These reactions, like that with methylamine, proceeded with evolution of hydrogen sulphide and were evidently straightforward displacements of the sulphur groups in dithio-β-*iso*indigo by the alkylamine residues.

The structures (III) for the new orange products were thus certain apart from questions of fine structure, *viz.*, (*a*) geometrical isomerism, (*b*) tautomerism, and (*c*) mesomerism.

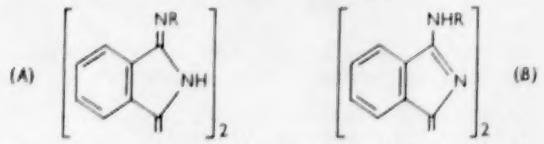
(*a*) Scale models, constructed on covalent atomic radii, indicated that the preferred

[4] Niederl, Kasanof, Kisch, and Subba Rao, *Mikrochemie*, 1949, **34**, 132.
[5] Drew and Kelly, *J.*, 1941, 630.

orientation of these molecules about the central double bond is *trans*. In the *cis*-form there would be hindrance between the benzene rings.

In agreement, the dialkylimino-β-*iso*indigos (III; R = Me, Bu, and CH_2Ph) were found not to form complexes with metals. Dithio-β-*iso*indigo does so,[6] but it seems that its metal derivatives may be mercaptides, rather than nitrogen-co-ordination complexes of the *cis*-form as suggested by Drew and Kelly.[6]

(*b*) The molecules (III) are potentially tautomeric: two of the possible forms are *A* and *B*, and a third is $\frac{1}{2}A + \frac{1}{2}B$. In order to gain information on the preferred positions of the active hydrogens, we prepared the derivative (V), which has a fixed bond structure, by condensing dithio-β-*iso*indigo with morpholine. Derivative (V) shows a principal maximum in the visible at **4800** Å with an inflexion at **4960** Å (see Table). The compounds (III; R = alkyl) have two main maxima in the visible at shorter wavelengths, in the regions **4400**—**4500** and **4660**—**4720** Å respectively. The phenyl derivative (III; R = Ph) has maxima



at **4680** and **4950** Å. By analogy with the 3-(substituted imino)-1-oxo*iso*indolines,[2,3] it seems likely that for the alkyl-substituted di-imino-β-*iso*indigos (III; R = Me, Bu, and CH_2Ph) the position of tautomeric equilibrium (in dioxan) is towards the di-1-*iso*indolinylidene form *A*, whereas for the phenyl-substituted compound (in the solvents named in the Table) it is towards the tautomeric form *B*.

(*c*) The light absorptions of the new β-*iso*indigo derivatives (see Table) are compatible with the bond structures assigned: there is no absorption at unexpectedly long wavelengths. Hence the compounds are evidently not appreciably mesomeric, and in that respect they differ markedly from the dipyrrolidinylidene described by Elvidge, Fitt, and Linstead.[7] Indeed most of the electronic isomers of the structures (III) would carry

Light absorptions.

Compound	Solvent	$\lambda_{max.}$ (Å)	ε
(III) R = Me ...	Dioxan	2280	49,400
		2930	10,900
		4410	34,200
		4660	30,300
R = Bu ...	,,	2280	44,700
		2940	8,200
		3330	6,100
		4500 }	32,400
		4720 }	
R = CH_2Ph	,,	2270	74,800
		2950	13,600
		4480	37,400
		4700	34,800
(III) R = Ph ...	Benzene	3150	11,600
		4640	33,100
		4940	31,000
	Ethanol	2460	47,500
		3040 }	19,500
		3170 }	
		4680	42,500
		4950	36,500
(V)	,,	2440	32,000
		2980 }	6,000
		3050 }	
		4800	28,400
		4960 *	24,800

All the solutions showed an intense green fluorescence under ultraviolet light. * Inflexion.

negative charges upon nitrogen, so that mesomerism in these molecules would not be favoured.

Evidence was sought for the existence of a more highly conjugated dehydro-form of the β-*iso*indigo derivatives, *viz.*, (VI). However, attempted dehydrogenation of the β-*iso*indigoid system (III) by means of lead dioxide, as with indigoids,[8] was unsuccessful, and attempts with quinones [9] were inconclusive.

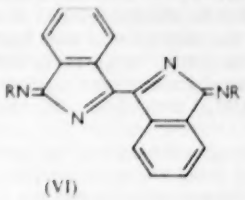
Formation of the β-iso*Indigoids.*—The reaction (II) ⟶ (III) could not be achieved with

[6] Drew and Kelly, *J.*, 1941, 625.
[7] Elvidge, Fitt, and Linstead, *J.*, 1956, 244.
[8] Madelung, *Annalen*, 1914, **405**, 58; Kalb, *Ber.*, 1909, **42**, 3642.
[9] Braude, Brook, and Linstead, *J.*, 1954, 3569; Eisner and Linstead, *J.*, 1955, 3749.

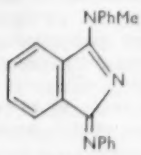
ammonia or aniline, *i.e.*, it could not be extended to the cases where R = R′ = R″ = H and R = R′ = R″ = Ph. Thus heating di-imino*iso*indoline (I) with ammonia at 200° gave only a trace of phthalocyanine, and most of the imidine (I) was recovered. Nothing identifiable was obtained after heating of 1 : 3-diphenylimino*iso*indoline (II; R′ = R″ = Ph) with aniline in ethyl carbitol (ethylene glycol ethyl ether) for 24 hr. Heating at 250° in ethanol for 72 hr. produced some complex changes; phthalamide and 1-oxo-3-phenylimino*iso*indoline were isolated and an accompanying trace of pigment was found to be a mixture of phthalocyanine with tetrabenzotriazaporphin. No other product was identified.

On the other hand, when 1 : 3-diphenylimino*iso*indoline (II; R′ = R″ = Ph), or better 1-imino-3-phenylimino*iso*indoline (II; R′ = H, R″ = Ph), was heated in ethyl carbitol with benzylamine, the dibenzylimino-β-*iso*indigo (III; R = CH_2Ph) was produced. This β-*iso*indigo derivative was also obtained, by means of benzylamine in boiling butanol, from 1 : 3-dimethylimino*iso*indoline (II; R′ = R″ = Me) and, interestingly, from 3-*N*-methylanilino-1-phenylimino*iso*indolenine (VII) [2] though in poor yield, but not apparently from 2-methyl-1 : 3-diphenylimino*iso*indoline (VIII).[3] The reaction liquors from the successful experiments contained benzaldehyde.

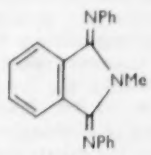
The displacement of a substituted imino-group by another in reactions of imidines with amines is known [1,3] and warrants no special comment here. Of particular significance, though, was the rôle of benzylamine in coupling the pyrrolic nuclei, itself apparently giving rise to benzaldehyde. In the favourable case of 1 : 3-dibenzylimino*iso*indoline (II; R′ =



(VI)



(VII)



(VIII)

R″ = CH_2Ph) already mentioned, an excess of benzylamine was required for the production of the β-*iso*indigo (III; R = CH_2Ph) in reasonable yield; no β-*iso*indigo derivative was formed from the *iso*indoline (II; R′ = R″ = CH_2Ph) merely by boiling it in butanol with pyridine, triethylamine, a *trace* of benzylamine, or with *cyclo*hexene alone or in the presence of palladium.

It seemed reasonable to suppose therefore that the formation of the β-*iso*indigo derivatives (III) from alkylimino*iso*indolines (II) (or phthalonitrile) and alkylamines involved a bimolecular reduction, the alkylamine being the specific hydrogen donor. When 1-imino-3-phenylimino*iso*indoline (II; R′ = H, R″ = Ph) and benzylamine were boiled together in purified *tert.*-amyl alcohol, the dibenzylimino-β-*iso*indigo (III; R = CH_2Ph) was formed in 48% yield. Treatment of the filtrate with dinitrophenylhydrazine reagent afforded the derivative of benzaldehyde to the extent of almost 2 molecular proportions, calculated on the imidine derivative consumed. In the absence of the imidine (II; R′ = H, R″ = Ph) no carbonyl compound was formed. Thus the benzylamine is indeed the bimolecular reducing agent in this reaction, functioning by the process $NH_2{\cdot}CH_2Ph \longrightarrow 2H + NH{:}CHPh \xrightarrow{H_2O} Ph{\cdot}CHO$) at the demand of the imidine. Methylamine and butylamine can fill a similar rôle but not, of course, ammonia or aniline. The various experimental results indicate that the overall reductive coupling process is 2(II) + 4H ⟶ (III) + $2NH_2R$. This type of reaction is being studied.

Experimental

Analyses were by Mr. F. H. Oliver and his staff of the microanalytical laboratory and the ultraviolet measurements by Mrs. A. I. Boston of the spectrographic laboratory of this Department.

Di-(3-methylimino-1-isoindolinylidene) (*Dimethylimino-β-isoindigo*) (III; R = Me).—(a) *Preparation.* (i) 1 : 3-Dimethylimino*iso*indoline [3] (II; R′ = R″ = Me) (3 g.) was heated with

dry methylamine (5 c.c.) and ethanol (15 c.c.) at 200° for 24 hr. After it had cooled, the solution deposited orange crystals (20 mg.), m. p. 308° (decomp.). From dioxan, *di*-(3-*methylimino*-1-iso*indolinylidene*) formed orange plates, m. p. 317—318° (decomp.) [Found: C, 75·3; H, 5·9; active H, (Zerewitinoff), 0·31, ($LiAlH_4$ in Bu_2O) 0·88, 0·91; N, 19·6%; *M* (Barger,[4] in acetone), 236, 258. $C_{18}H_{14}N_4$ requires C, 75·0; H, 5·6; 2 active H, 0·70; N, 19·4%; *M*, 288]. Concentration of the reaction mother-liquors under reduced pressure afforded 1 : 3-dimethyliminoisoindoline (2·7 g.), m. p. and mixed m. p. 169°.

(ii) Phthalonitrile (5 g.) was heated with methylamine (12 c.c.) and ethanol (15 c.c.) at 100° for 24 hr. and then at 200° for 20 hr. The solution was filtered hot, and the orange product (1·7 g., 28%), m. p. *ca.* 312° (decomp.), was washed with methanol and recrystallised from dioxan, to afford the dimethylimino-β-*iso*indigo as orange plates, m. p. and mixed m. p. 317—318° (decomp.). The reaction liquors were treated with charcoal and concentrated under reduced pressure. Addition of benzene to the residual syrup caused 1 : 3-dimethyliminoisoindoline to crystallise (2 g.; m. p. and mixed m. p. 165°).

(b) *Oxidative hydrolysis.* The dimethylimino-β-*iso*indigo (189 mg.) was warmed on the steam-bath with 2N-nitric acid (6 c.c.) for 2—3 min. The clear solution was chilled in ice, and after 15 min. the precipitated phthalimide was collected, washed, and dried (186 mg., 94%; m. p. and mixed m. p. 234°). The filtrate was evaporated to dryness and the residue treated with alkali: methylamine was recognised by smell.

Di-(3-*phenylimino*-1-iso*indolinylidene*) (III; R = Ph).—This was prepared by Drew and Kelly's method [5] from dithio-β-*iso*indigo.

Di-(3-*butylimino*-1-iso*indolinylidene*) (III; R = Bu).—(i) 1 : 3-Di-imino*iso*indoline [1] (I) (5 g.) was converted with *n*-butylamine (10 c.c., redistilled) in ethanol (15 c.c.) at 100° into the 1 : 3-dibutylimine (II; R = R′ = Bu) (cf. ref. 2), and the solution was then kept at 200° for 24 hr. The cooled solution deposited orange-red crystals (1·5 g., 24%), m. p. 239° (decomp.). From dioxan (charcoal), *di*-(3-*butylimino*-1-iso*indolinylidene*) formed orange prisms, m. p. 244° (decomp.) [Found: C, 77·4; H, 7·7; active H ($LiAlH_4$), 0·63, 0·58; N, 15·2. $C_{24}H_{28}N_4$ requires C, 77·4; H, 7·6; 2 active H, 0·54; N, 15·1%].

(ii) Heating of di-imino*iso*indoline (5 g.) with butylamine (10 c.c.) in butanol (15 c.c.) for 72 hr. afforded the dibutylimino-β-*iso*indigo (1·5%) and (from the mother-liquors, by evaporation) 1 : 3-dibutyliminoisoindoline (58%), identified by m. p.s and mixed m. p.s.

(iii) Dithio-β-*iso*indigo [6] (IV) (95 mg.) was heated under reflux with butylamine (4 c.c.) for 1 hr. The solution was evaporated to 1 c.c., diluted with ether (100 c.c.), and kept overnight at 0°. Orange crystals of dibutylimino-β-*iso*indigo (58 mg., 48%), m. p. and mixed m. p. 242° (decomp.), separated.

Di-(3-*benzylimino*-1 iso*indolinylidene*) (III; R = CH_2Ph).—(a) *Preparation.* (i) 1 : 3-Di-benzyliminoisoindoline [3] (II; R′ = R″ = CH_2Ph) (300 mg.), butanol (5 c.c.), and benzylamine (2 c.c.) were heated together under reflux for 24 hr. When the solution had been concentrated under reduced pressure to 3 c.c. and cooled, orange crystals (71·5 mg., 35%), m. p. 299° (decomp.), separated. Recrystallisation of the product from dioxan afforded orange-red felted needles of di-(3-benzylimino-1-*iso*indolinylidene), m. p. 302° (decomp.) with darkening from *ca.* 280° (Found: C, 81·9; H, 5·7; N, 12·8. $C_{30}H_{24}N_4$ requires C, 81·8; H, 5·5; N, 12·7%).

(ii) Di-imino*iso*indoline [1] (I) (8 g.), benzylamine (16 c.c.), and butanol (50 c.c.) were heated together under reflux for 56 hr. Ammonia was rapidly evolved initially and the solution soon became dark red. From the cold solution, the dibenzylimino-β-*iso*indigo separated as orange crystals (2 g., 17%), m. p. 284° (decomp.), and m. p. 302° (decomp.) after recrystallisation from dioxan.

(iii) Dithio-β-*iso*indigo [6] (IV) (114 mg.) and benzylamine (4 c.c.) were heated together under reflux. There was a slow evolution of hydrogen sulphide. After 1 hr., the brown solution was cooled and poured into ether (40 c.c.), and the orange crystalline precipitate (65 mg.) was subsequently collected. Addition of more ether (40 c.c.) and cooling to 0° overnight afforded a second crop (45 mg.): the total yield was 65%, and the m. p. and mixed m. p. 299° (decomp.).

(b) *Oxidative hydrolysis.* Warming the dibenzylimino-β-*iso*indigo (319 mg.) with 2N-nitric acid (10 c.c.) on the steam-bath for 35 min. afforded a pale orange solution containing suspended solid: the mixture smelled strongly of benzaldehyde. The mixture was cooled in ice and filtered. Extraction of the solid (286 mg.) with hot water yielded needles of phthalimide, m. p. and mixed m. p. 232°.

Attempted Thiohydrolyses.—The dibenzylimino-β-*iso*indigo (214 mg.) was boiled in dioxan (15 c.c.) with aqueous ammonium polysulphide (5 c.c.; 16%) for 18 hr. After cooling of the solution, the β-*iso*indigo derivative was recovered (209 mg.), identified by m. p. and mixed m. p.

The dimethylimino-β-*iso*indigo was likewise unaffected by similar treatment. The solution did not develop a purple colour.

Attempted Metallation.—(i) There was no change in visible light absorption when solutions of the imino-β-*iso*indigos in pyridine and dimethylformamide were mixed with nickel and copper acetates in these solvents.

(ii) The dibenzylimino-β-*iso*indigo was recovered after being heated under reflux in pyridine with anhydrous cobalt acetate for 1 hr.

*Di-(3-morpholino-1-iso**indoleninylidene*) (V).—(a) *Preparation.* Dithio-β-*iso*indigo (IV) (0·4 g.) and morpholine (5 c.c.) were heated together under reflux for 2·5 hr. Hydrogen sulphide was evolved. As the solution cooled, it deposited orange crystals (0·27 g.), m. p. 314—315° (decomp.). From dioxan *di-(3-morpholino-1-iso**indoleninylidene*) formed orange needles, m. p. 319—320° (decomp.) (Found: C, 72·1; H, 6·2; N, 14·3. $C_{24}H_{24}O_2N_4$ requires C, 72·0; H, 6·0; N, 14·0%).

(b) *Oxidative hydrolysis* [with M. E. Bagley]. The preceding derivative (270 mg.) was heated with 2N-nitric acid at 100° for 5 min. The mixture was then cooled in ice. The solid (190 mg., 1·79 mols.) was identified as phthalic acid (positive fluorescein reaction) by mixed m. p. 192—195°.

Attempted Dehydrogenation[8] *of Dibenzylimino-β-iso**indigo* (III; R = CH_2Ph).—The β-*iso*indigo (0·34 g.), lead dioxide (2·8 g.), and anhydrous calcium chloride (2 g.) were boiled together in benzene (50 c.c.) for 5 hr. Evaporation of the filtrate to dryness afforded a reddish solid (215 mg.), contaminated with traces of lead compounds. The solid did not depress the m. p. of dibenzylimino-β-*iso*indigo. In dioxan solution the product and the starting material had closely similar light absorption characteristics. Addition of acetic acid to a second reaction mixture caused destruction of the β-*iso*indigoid.

*Attempted Reaction of Di-imino**iso**indoline* (I) *with Ammonia under Vigorous Conditions.*—Phthalonitrile (3 g.) was converted with ammonia (7 c.c. of liquid) in dry ethanol (20 c.c.) at 100° into di-imino*iso*indoline (cf. ref. 1), and the solution was then kept at 200° for 24 hr. Filtration of the solution from phthalocyanine (40 mg.; identified spectroscopically) and concentration of the filtrate under reduced pressure afforded 1 : 3-di-imino*iso*indoline (3·3 g., 97%), m. p. and mixed m. p. 195° (decomp.).

*Action of Aniline on Phenylimino**iso**indolines under Vigorous Conditions.*—(i) Phthalonitrile (6 g.) was treated with aniline (15 c.c.) in ethanol (15 c.c.) at 100° for 24 hr. as for conversion into 1 : 3-diphenylimino*iso*indoline (II; R′ = R″ = Ph) (cf. ref. 2), and the solution was then heated at 200—250° for 72 hr. A greenish solid *A* (0·51 g.) was filtered from the ammoniacal liquor which was then concentrated under reduced pressure to a syrup. Treatment of the latter with ether afforded a yellowish-brown solid *B* (87 mg.), m. p. 224°. The filtrate was evaporated, the residue taken up in methanol, and the solution treated with charcoal and evaporated. Treatment of the sticky solid residue with ether (100 c.c.) then gave a yellow powder *C* (2·9 g.), m. p. 157° (decomp.).

Solid *A* was warmed with methanol (200 c.c.), and the solution, filtered from insoluble pigment (28 mg.), shown spectroscopically to be a mixture of phthalocyanine and tetrabenzotriazaporphin[10] ($\lambda_{max.}$ 693 > 665, 650 > 595 ≫ 634, 619). Evaporation and cooling of the filtrate yielded a crystalline solid (352 mg.), m. p. 223°, identical with *B*.

Solid *B* was recrystallised from methanol–butanol, affording phthalamide, m. p. and mixed m. p. 224° (Found: N, 17·2. Calc. for $C_8H_6O_2N_2$: N, 17·1%).

Solid *C* was crystallised extractively from light petroleum (b. p. 60—80°) and then from ethanol ordinarily. 1-Oxo-3-phenylimino*iso*indoline was obtained, having m. p. 168° undepressed by authentic material.[1]

(ii) 1-Imino-3-phenylimino*iso*indoline[2] (II; R′ = H, R″ = Ph) (0·5 g.) and aniline (3 c.c.) in boiling ethyl carbitol (3 c.c.) for 24 hr. gave only 1 : 3-diphenylimino*iso*indoline (294 mg.), m. p. and mixed m. p. 129—130°.

(iii) From a similar experiment with 1 : 3-diphenylimino*iso*indoline nothing identifiable was obtained.

Related Experiments.—No dibenzylimino-β-*iso*indigo was obtained by boiling 1 : 3-dibenzylimino*iso*indoline (0·3 g.) in butanol (5 c.c.) for 24 hr. alone, or with a trace of benzylamine (5 mg.), with triethylamine (2 c.c.), with pyridine (2 c.c.), with *cyclo*hexene, or with *cyclo*hexene (5 c.c.) and 5% palladium–charcoal (10 mg.).

*Action of Benzylamine on Phenylimino**iso**indolines.*—(i) 1 : 3-Diphenylimino*iso*indoline (II; R′ = R″ = Ph) (0·5 g.) and benzylamine (3 c.c.) were boiled in ethyl carbitol (3 c.c.) for 24 hr.

[10] Barrett, Linstead, and Tuey, *J.*, 1939, 1809.

The solution was evaporated to 2 c.c. under reduced pressure, and benzene (5 c.c.) was added. During 3 weeks, orange crystals of dibenzylimino-β-*iso*indigo (III; R = CH_2Ph) (18 mg.) separated; it had m. p. 285° (decomp.), raised after a crystallisation from dioxan to 301° (decomp.) undepressed by authentic material.

(ii) 1-Imino-3-phenyliminoisoindoline (0·5 g.) and benzylamine (3 c.c.) in boiling ethyl carbitol (3 c.c.) similarly gave dibenzylimino-β-*iso*indigo (53 mg.), m. p. 286° (decomp.), which after crystallisation from dioxan had m. p. and mixed m. p. 301° (decomp.).

(iii) 1 : 3-Dimethyliminoisoindoline (1·73 g.) was heated under reflux with benzylamine (2·14 g.) in butanol (5 c.c.) for 48 hr. The solution, which smelled of benzaldehyde, was evaporated to 3 c.c. and diluted with ether (40 c.c.), and 2 weeks later the yellow crystals were collected [32 mg.; m. p. 290° (decomp.)]. After being recrystallised from dioxan, the product had m. p. 295° (decomp.) undepressed by dibenzylimino-β-*iso*indigo but depressed by dimethylimino-β-*iso*indigo.

(iv) 3-*N*-Methylanilino-1-phenyliminoisoindolenine[2] (VII) (0·5 g.), butanol (5 c.c.), and benzylamine (3 c.c.) were boiled together for 17 hr., and the solution was then evaporated under reduced pressure to a small volume, and ether was added. After 24 hr., orange crystals (71 mg.) had separated; these had m. p. 299° (with some previous softening) undepressed by dibenzylimino-β-*iso*indigo (III; R = CH_2Ph). The filtrate was diluted with chloroform and washed with aqueous hydrochloric acid. The chloroform was evaporated and the residue extracted with ether several times. Evaporation of the ether and treatment of the oily residue in ethanol with an ethanolic sulphuric acid solution of 2 : 4-dinitrophenylhydrazine at once afforded the derivative of benzaldehyde (292 mg., m. p. and mixed m. p. 232—233°).

(v) A solution of 1-imino-3-phenyliminoisoindoline (500 mg.) in *tert.*-amyl alcohol (3 c.c.; previously refluxed with sodium and distilled) was boiled with benzylamine (3 c.c.) for 48 hr. and then kept at room temperature for 48 hr. The orange crystalline product (242 mg., 48%) had m. p. 299° (decomp.) not depressed by dibenzylimino-β-*iso*indigo. Treatment of the filtrate with an excess of ethanolic 2 : 4-dinitrophenylhydrazine sulphate afforded benzaldehyde 2 : 4-dinitrophenylhydrazone (621 mg., 96%), m. p. and mixed m. p. 237°.

(vi) No benzaldehyde derivative was obtained from a duplicate experiment in which the 1-imino-3-phenyliminoisoindoline had been omitted.

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801. *Triterpenoids. Part XXII.* The Constitution and Stereochemistry of Masticadienonic Acid.†*

By D. H. R. Barton and E. Seoane.

The isolation of a new triterpenoid acid, masticadienonic acid, from gum mastic is reported. By degradation experiments this acid has been characterised as a derivative of tirucall-7-en-3β-ol. It contains a ketone grouping at the customary 3-position and has an αβ-unsaturated acid function at the terminus of the $C_{(8)}$-side chain. On the basis of this and other evidence the constitution and stereochemistry of the acid have been elucidated.

Although gum mastic has been an important article of commerce for centuries, its scientific chemistry has scarcely received consideration. Our own interest in this material was first stimulated by Mr. J. S. Mills of the National Gallery, who kindly informed us that it probably contained triterpenoid constituents.[1] We express our best thanks to Mr. Mills for this information and for his valuable advice in the initial stages of our investigation.

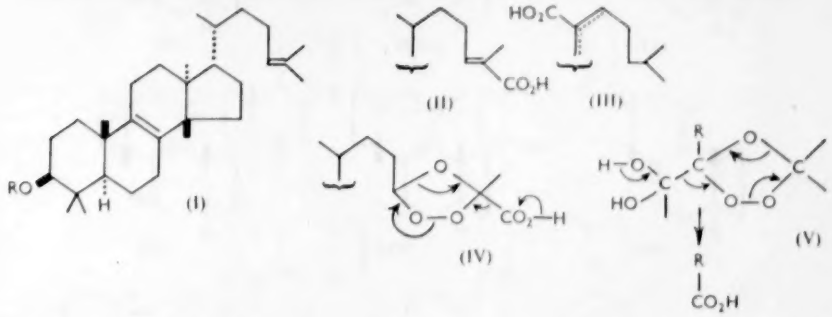
* Part XXI, *J.*, 1956, 788.

† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] See Mills and Werner, *Nature*, 1952, **169**, 1064; cf. *idem*, *J.*, 1955, 3132; Mills, *Chem. and Ind.*, 1956, 189.

Gum mastic was examined by Tschirsh and Reutter [2] and by Casparis and Naef,[3] but it is extremely improbable that any of the compounds obtained by these workers was homogeneous. A crystalline unnamed acid constituent of the composition $C_{30}H_{46}O_3$ was reported recently by Mladenovic.[4] This acid may be identical with our masticadienonic acid described in the sequel, but the absence of the record by Mladenovic of any derivatives and of any physical constant except the m. p. prevents a definite decision.

After removal of polymeric hydrocarbon, gum mastic was separated into fractions which were severally neutral, acidic to sodium carbonate, and acidic to sodium hydroxide.



This paper is concerned with crystalline materials isolated from the first two of these fractions. It is hoped to report later on a crystalline acid that we have obtained from the third fraction.

Hydrolysis of the neutral fraction gave a product which was mainly neutral. Chromatography over alumina then afforded crystalline material which was identified as tirucallol (I; R = H).[5,6,7]

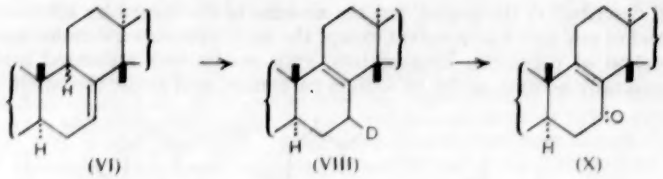
The acid fraction soluble in aqueous sodium carbonate was chromatographed over silica, to give a beautifully crystalline acid, $C_{30}H_{46}O_3$, which we designate masticadienonic acid. This was characterised as αβ-unsaturated by its ultraviolet absorption spectrum. The derived methyl ester had a similar spectrum and gave infrared bands at **1712** [superimposed ketone (see further below) and αβ-unsaturated ester] and **1650** cm.$^{-1}$ (ethylenic linkage of αβ-unsaturated ester grouping). The presence of a ketone grouping was shown by the preparation of a 2 : 4-dinitrophenylhydrazone and by reduction with sodium borohydride which afforded masticadienolic acid. Reduction with lithium aluminium hydride gave the expected masticadienediol.

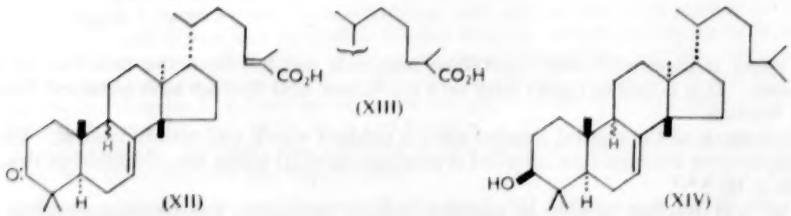
The conjugated ethylenic linkage of masticadienonic acid was readily hydrogenated over palladium to furnish dihydromasticadienonic acid, further characterised as its methyl ester. The ultraviolet absorption spectra of these compounds showed the disappearance of the conjugated absorption but the retention of absorption equivalent to one non-conjugated ethylenic linkage (see further below). The methyl ester gave bands at **1738** (methoxycarbonyl) and **1710** cm.$^{-1}$ (six-ring ketone) in the infrared. Reduction of dihydromasticadienonic acid with sodium borohydride afforded dihydromasticadienolic acid, converted by conventional methods into the methyl ester and thence into the methyl ester acetate.

That masticadienonic acid contains two ethylenic linkages has already been implied (see above). The second, non-conjugated linkage gives a positive tetranitromethane test as shown by all compounds mentioned above. In specific confirmation of this feature

[2] Tschirsh and Reutter, *Arch. Pharm.*, 1904, **242**, 104.
[3] Casparis and Naef, *Pharm. Acta Helv.*, 1934, **9**, 19.
[4] Mladenovic, *Acta Pharm. Yugoslav.*, 1953, **3**, 1.
[5] Haines and Warren, *J.*, 1949, 2554; 1950, 1562.
[6] Barbour, Lourens, Watling, and Warren, *Chem. and Ind.*, 1955, 226; *J.*, 1955, 2194.
[7] Arigoni, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1955, **38**, 222; Ménard, Wyler, Hiestand, Arigoni, Jeger, and Ruzicka, *ibid.*, p. 1517.

treatment of methyl dihydromasticadienolate acetate with ozone afforded a nicely crystalline epoxide (negative tetranitromethane test and no ultraviolet absorption) to which further reference is made below.





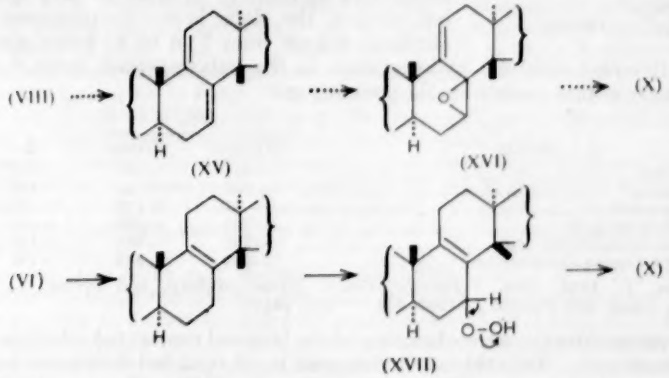
With the nature of the functional groups established it follows from the composition that masticadienonic acid must be tetracyclic. A possible relation to other tetracyclic triterpenoids was first inferred from the following experiments. Oxidation of methyl dihydromasticadienolate acetate with selenium dioxide afforded, with loss of two hydrogen atoms, a conjugated diene, the ultraviolet absorption spectrum of which ($\lambda_{max.}$ 240 mμ) showed that the diene system must be distributed over two rings. The same diene resulted from the epoxide mentioned above under mild acid conditions of dehydration. Attempted catalytic hydrogenation of methyl dihydromasticadienolate acetate in acetic acid solution over platinum gave an isomer, further characterised by hydrolysis to the parent hydroxy-acid. On oxidation with chromic acid the methyl ester acetate afforded a yellow diketo-derivative the ultraviolet absorption of which ($\lambda_{max.}$ 270 mμ) indicated the presence of the fully *transoid* ene-1 : 4-dione system so common in tetracyclic triterpenoids.[8] In agreement with the postulated ene-1 : 4-dione system reduction with zinc dust and acetic acid afforded a saturated diketone with no high-intensity ultraviolet absorption.

The main problem at this stage of the investigation was to convert the carboxyl group of masticadienonic acid, or a suitable derivative, into methyl. This was effected as follows. Reduction either of dihydromasticadienonic acid, or of its methyl ester, with lithium aluminium hydride gave dihydromasticadienediol. Attempted hydrogenation of this compound, after acetylation, gave on alkaline hydrolysis *iso*dihydromasticadienediol. Treatment of dihydromasticadienediol with toluene-*p*-sulphonyl chloride and pyridine afforded, according to the duration of the reaction, either a mono- or a di-toluene-*p*-sulphonate. Both of these compounds, or a mixture thereof, furnished on further reduction with lithium aluminium hydride a secondary alcohol, $C_{30}H_{52}O$, m. p. 108—110°, $[\alpha]_D$ −53°. Acetylation gave the acetate and this was rearranged smoothly over platinum under the

[8] For an excellent review see Halsall and Jones, *Fortschr. Chem. org. Naturstoffe*, 1955, **12**, 44.

conditions specified above to afford tirucallenol acetate (I; R = Ac). The identity was further confirmed by hydrolysis to tirucallenol (I; R = H). These experiments establish the nature of the carbon skeleton of masticadienonic acid and the position of the ketone grouping. The αβ-unsaturated acid function can only be placed as in (II) or (III). A decision in favour of (II) was secured by ozonolysis which gave one mol. of acetic acid. Such ozonolyses, employed recently in the work on tenulin,[9] are of the mechanistic types (electron release by O–H bond heterolysis) exemplified in (IV) and (V). These mechanisms also explain satisfactorily some recent results by Knights and Waight.[10]

There remains to be defined the exact position of the nuclear ethylenic linkage. This

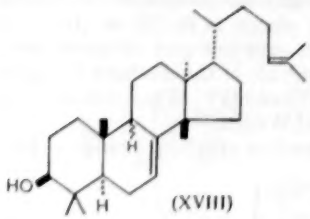


must be placed either at position 7 : 8 [as in (VI)] or at position 9 : 11 [as in (VII)]. A decision on this point was reached as follows. If the rearrangement of the nuclear ethylenic linkage were conducted over platinum in deuterium instead of hydrogen then one (or more) deuterium atoms would be introduced to give (VIII) or (IX). Now it has been shown [11] that treatment of euphenyl acetate (as I; R = Ac) [11, 12, 13] in ethyl acetate solution with ozone followed by a ferrous-ion wash affords a relatively good yield of 7-oxoeuphenyl acetate (as X). Now if this reaction were to be applied to the deuterated product (VIII) or (IX) one would obtain either (X), which would be free from deuterium, or (XI), which would retain its deuterium. In fact deuterogenation of methyl dihydromasticadienolate acetate over platinum in $CH_3 \cdot CO_2D$ gave a product containing just over one atom of deuterium.[14] This was oxidised by ozone to furnish the 7-ketone which contained no deuterium. The position of the ethylenic linkage is therefore established as in (VI) and complete structures can now be written for masticadienonic acid (XII), dihydromasticadienonic acid (XIII), and related compounds including the intermediate alcohol, m. p. 108—110° (see above) (XIV).

There is, however, a possible fallacy in the above proof of constitution which requires comment. If the ozonolysis of the deutero-compound (VIII) were to proceed through the corresponding diene (XV), its derived epoxide (XVI), and rearrangement,[15] then deuterium would be removed from both positions 7 and 11. Such a possibility was rejected by showing that methyl dehydrodihydromasticadienolate acetate (as XV), the preparation of which has been mentioned above, gave no 7-oxo-derivative on ozonolysis. Our interpretation of the mechanism of genesis of the ketone (X) is that it probably proceeds through the hydroperoxide (XVII) as indicated.

[9] Barton and de Mayo, *J.*, 1956, 142.
[10] Knights and Waight, *J.*, 1955, 2830.
[11] Barton, McGhie, Pradhan, and Knight, *J.*, 1955, 876.
[12] *Idem*, *Chem. and Ind.*, 1954, 1325.
[13] Arigoni, Viterbo, Dünnenberger, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2306.
[14] For method of determination see Barton, Campos Neves, Cookson, and Eglinton, to be published.
[15] Cf., *inter al.*, Birchenough and McGhie, *J.*, 1950, 1249; Mijovic, Voser, Heusser, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 964.

Recently the constitution and stereochemistry (XVIII) have been proposed for butyrospermol.[8, 16, 17] As would be expected there is a close relation between this compound and masticadienonic acid so far as the reactions of the nucleus are concerned. There is also the same negative molecular-rotation difference on oxidation to the ketone (see Table) and the same anomalous behaviour (see Experimental) of the latter towards the Zimmermann reagent.[18] In addition the various molecular-rotation correlations between the two series are in satisfactory agreement; in order to save space we do not present the data here. Rearrangement of the ethylenic linkage from 7 : 8 to 8 : 9 has already been noted on attempted catalytic hydrogenation in the butyrospermol series,[16] behaviour which is exactly as that recorded in the present paper.



(XVIII)

Alcohol	[M] Alcohol	[M] Ketone	Δ	Refs.
*cyclo*Artenol	+204°	+102°	−102°	*a*
*cyclo*Laudenol	+206	+ 83	−123	*b*
Butyrospermol	− 51	−170	−119	*c*
Masticadienolic acid	−201	−345	−144	*d*
Dihydromasticadienolic acid	−229	−365	−136	*d*
Methyl dihydromasticadienolate	−203	−353	−150	*d*

[a] Barton, *J.*, 1951, 1444. [b] Bentley, Henry, Irvine, Mukerji, and Spring, *J.*, 1955, 596. [c] Heilbron, Jones, and Robins, *J.*, 1949, 444. [d] This paper.

Finally we consider the stereochemistry of the terminal conjugated ethylenic linkage of masticadienonic acid. The evidence on this point is not rigid, but it seems to indicate that the configuration is the more stable *trans*, as in formula (XII). Thus masticadienolic acid was recovered unchanged after treatment with alkali under conditions considerably more drastic than those required [19] for a comparable *cis* ⟶ *trans* αβ-unsaturated acid isomerisation. Also the subtraction of the ultraviolet absorption curve of dihydromasticadienonic acid from that of masticadienonic acid (both determinations at the same concentration in acidified ethanol) gave a curve showing $\lambda_{max.}$ 218 mμ (ε 10,300) for the true absorption of the αβ-unsaturated acid function. This absorption is more intense than that recorded [20] for any *cis*-acid, but is fully comparable with that for a *trans*-configuration.

Experimental

Except as stated, rotations were determined in $CHCl_3$ solution. Ultraviolet absorption spectra were taken, unless specified to the contrary, in EtOH solution with the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and his associates on CCl_4 solutions. Silica gel for chromatography was obtained from Messrs. Hopkin and Williams Ltd. Light petroleum of b. p. 40—60° was used throughout, unless stated to the contrary.

Fractionation of Gum Mastic.—Finely powdered commercial gum mastic (480 g.) in ether (500 ml.) was diluted with methanol (3·5 l.) and left overnight. After decantation from the insoluble residue the solution was evaporated *in vacuo* and the residue again dissolved in ether (500 ml.) and diluted with methanol (3·5 l.). The operation was repeated (three times in all) until the gum was freely soluble in the ether–methanol mixture. The residue from this process, in ether (4 l.), was repeatedly extracted (*a*) with sodium carbonate solution (5%; 1 l. : emulsion), and (*b*) with 0·5N-sodium hydroxide (700 ml.). After acidification and re-extraction into ether there were obtained (*a*) sodium carbonate-soluble (and emulsion) acids (86 g.), (*b*) sodium hydroxide-soluble acids (24 g.), and (*c*) neutral residue (170 g.).

Examination of Neutral Fraction.—The neutral fraction (170 g.) in absolute ethanol (1 l.) was treated with sodium hydroxide (75 g.) in ethanol (1·5 l.) under reflux for 3 hr. Most of the

[16] Dawson, Halsall, Jones, Meakins, and Phillips, *Chem. and Ind.*, 1955, 918.
[17] Irvine, Lawrie, McNab, and Spring, *ibid.*, p. 626.
[18] Personal communication from Professor E. R. H. Jones, F.R.S., and Dr. T. G. Halsall.
[19] Myers, *J. Amer. Chem. Soc.*, 1951, **73**, 2100.
[20] Adams and van Duuren, *ibid.*, 1953, **75**, 4632.

solvent was removed *in vacuo* and the concentrated solution diluted with water and extracted with ether. This gave a hydrolysed neutral fraction (145 g.). A portion of this material (10 g.) was treated with pyridine (50 ml.) and acetic anhydride (25 ml.) at room temperature overnight, and the oily mixed acetates produced were chromatographed over alumina (300 g.) in benzene (10 ml.) and light petroleum (200 ml.). Elution with the same solvent mixture, increasing the proportion of benzene to 100%, gave 60 fractions of which fractions 4—10 gave a crystalline compound. For purification these fractions were hydrolysed with 5% ethanolic potassium hydroxide under reflux for 2 hr. The neutral product then crystallised well from methanol (300 mg.) and was identified as tirucallol by m. p. (135—136°), rotation {$[\alpha]_D$ +2° (*c* 1·10 in C_6H_6), −9° (*c* 1·06)}, and analysis (Found : C, 84·15; H, 11·9. Calc. for $C_{30}H_{50}O$: C, 84·45; H, 11·8%). Acetylation in the usual way gave (from methanol) tirucallyl acetate, identified by m. p. (159—161°), rotation {$[\alpha]_D$ −14° (*c* 1·24 in C_6H_6), −4° (*c* 1·16)}, and analysis (Found : C, 81·65; H, 11·0. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Benzoylation in the usual way afforded (from chloroform–methanol) tirucallyl benzoate, identified by m. p. (145—147°) and rotation {$[\alpha]_D$ +32° (*c* 1·11)}. For these compounds Haines and Warren [5] recorded the constants : m. p. 133—135°, $[\alpha]_D$ +5°, m. p. 164°, $[\alpha]_D$ −17°, m. p. 149—151°, $[\alpha]_D$ +11°, for the alcohol, acetate, and benzoate respectively (all rotations in C_6H_6).

Hydrogenation of the tirucallyl acetate in acetic acid solution over platinum gave tirucallenyl acetate, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ −12° (*c* 1·04 in C_6H_6), −1° (*c* 1·35)}, and analysis (Found : C, 81·45; H, 11·45. Calc. for $C_{32}H_{54}O_2$: C, 81·65; H, 11·55%). Alkaline hydrolysis afforded tirucallenol, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +3° (*c* 1·05 in C_6H_6), −9° (*c* 1·00)}.

Masticadienonic Acid.—The acid fraction (*a*) (see above) (10 g.) in 1 : 1 benzene–light petroleum (300 ml.) was chromatographed over silica gel (400 g.) (20 fractions in all). Elution with benzene and with 1 : 3 ether–benzene gave *masticadienonic acid* (1·4 g.), m. p. 178° (from ether–light petroleum), $[\alpha]_D$ −76° (*c* 1·35), $\lambda_{max.}$ 214 mμ (ε 12,500) [Found : C, 79·05; H, 10·0; equiv. (potentiometric), 451, 453. $C_{30}H_{46}O_3$ requires C, 79·25; H, 10·2%; equiv., 455]. The acid gave a positive tetranitromethane test, but a very weak Zimmermann colour.

Treatment of masticadienonic acid (108 mg.) in methylene dichloride (20 ml.) at −25° with ozone (excess), addition of water, and separation of the aqueous layer gave a solution which on distillation afforded 0·82 mol. of volatile acid. This was converted into the *p*-bromophenacyl ester and identified as the acetic acid derivative by m. p., mixed m. p. and ultraviolet absorption spectrum ($\lambda_{max.}$ 257 mμ; ε 18,000; identical with that of an authentic specimen).

Treatment of masticadienonic acid with diazomethane in the usual way furnished *methyl masticadienonate*, m. p. (from methanol) 125°, $[\alpha]_D$ −77° (*c* 0·64), $\lambda_{max.}$ 214 mμ (ε 12,700) (Found : C, 79·75; H, 10·0. $C_{31}H_{48}O_3$ requires C, 79·45; H, 10·3%).

Masticadienonic acid gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 245° (from chloroform–ethanol), $\lambda_{max.}$ 370 mμ (ε 24,400 in $CHCl_3$) (Found : C, 68·1; H, 7·6; N, 9·15. $C_{36}H_{50}O_6N_4$ requires C, 68·1; H, 7·95; N, 8·85%).

Reduction of masticadienonic acid (135 mg.) in methanol (30 ml.) with sodium borohydride (90 mg.) in water (1 ml.) overnight at room temperature gave *masticadienolic acid*, m. p. 200—201° (from methanol), $[\alpha]_D$ −44° (*c* 1·12), $\lambda_{max.}$ 212 mμ (ε 12,100) (Found : C, 78·7; H, 10·35. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Reduction of masticadienonic acid (416 mg.) in dry ether (50 ml.) with lithium aluminium hydride (900 mg.) in the same solvent (100 ml.) under reflux for 3 hr. afforded *masticadienediol*, m. p. 186—187° (from benzene) $[\alpha]_D$ −51° (*c* 1·46), $\lambda_{max.}$ 205 mμ (ε 9700) (Found : C, 81·7; H, 11·05. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

Masticadienolic acid (140 mg.) was refluxed with ethanolic potassium hydroxide [23] (28%; 2 ml.) for 5 hr. and also for 11 hr. In both cases starting material (100 mg.) was recovered and identified by m. p., mixed m. p., and rotation. Chromatography over silica gel did not disclose a second acid.

Dihydromasticadienonic Acid.—Masticadienonic acid (169 mg.) in ethyl acetate (40 ml.) was hydrogenated over palladised charcoal (10%; 150 mg.) (uptake of hydrogen, 1 mol.), to give *dihydromasticadienonic acid*, m. p. 156° (from aqueous methanol), $[\alpha]_D$ −80° (*c* 1·13), $\lambda_{max.}$ 207, 290 mμ (ε 4700, 40 respectively) (Found : C, 79·1; H, 10·8. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Treatment with ethereal diazomethane in the usual way gave *methyl dihydromasticadienonate*, m. p. 90° (after chromatography over alumina, elution with 1 : 2 benzene–light petroleum and crystallisation from aqueous methanol), $[\alpha]_D$ −75° (*c* 1·71) (Found : C, 79·1; H, 10·65. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%).

Dihydromasticadienolic Acid.—Dihydromasticadienonic acid (398 mg.) in methanol (40 ml.)

was treated overnight at room temperature with sodium borohydride (240 mg.) in water (2 ml.). Crystallisation of the product from methanol gave *dihydromasticadienolic acid*, m. p. 208° (from methanol), $[\alpha]_D$ −50° (*c* 1·23) (Found : C, 78·55; H, 10·8. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Treatment with diazomethane in the usual way afforded *methyl dihydromasticadienolate*, m. p. 117—118° (from aqueous methanol), $[\alpha]_D$ −43° (*c* 1·01) (Found : C, 78·75; H, 10·85. $C_{31}H_{52}O_3$ requires C, 78·75; H, 11·1%). Acetylation with pyridine–acetic anhydride overnight at room temperature gave *methyl dihydromasticadienolate acetate*, m. p. 92—93° (from aqueous methanol after filtration over alumina in 1 : 4 benzene–light petroleum), $[\alpha]_D$ −30° (*c* 1·01), $\lambda_{max.}$ 205 mμ (ε 5800) (Found : C, 76·4; H, 10·4. $C_{33}H_{54}O_4$ requires C, 77·0; H, 10·55%).

This methyl ester acetate (77 mg.) in ethanol (10 ml.) was refluxed with selenium dioxide (200 mg.), and the development of the ultraviolet chromophore determined (3 hr., ε 2100; 6 hr., ε 3000; 18 hr., ε 10,000; all readings at $\lambda_{max.}$ 240 mμ). The product was chromatographed over alumina in benzene–light petroleum mixtures, to give *methyl dehydrodihydromasticadienolate acetate*, m. p. 94—95° (from aqueous methanol), $[\alpha]_D$ −133° (*c* 1·21), $\lambda_{max.}$ 240 mμ (ε 15,800) (Found : C, 74·9; H, 9·7. $C_{33}H_{52}O_4,H_2O$ requires C, 74·65; H, 10·25%).

Treatment of methyl dihydromasticadienolate acetate (200 mg.) in ethyl acetate (10 ml.) with ozone at −25°, until the tetranitromethane test was negative (30 min.), gave *methyl dihydromasticadienolate acetate epoxide* (147 mg.), m. p. 152—154° (from methanol), $[\alpha]_D$ −57° (*c* 1·00) (Found : C, 74·7; H, 10·05. $C_{33}H_{54}O_5$ requires C, 74·65; H, 10·25%). This epoxide (100 mg.) in chloroform (2 ml.) was treated for 5 min. with dry hydrogen chloride and left at room temperature for 2 hr. The product was chromatographed over alumina (6 g.) in 1 : 3 benzene–light petroleum to give (five fractions : m. p., mixed m. p., and ultraviolet absorption spectrum) the dehydro-ester referred to above.

Methyl iso*Dihydromasticadienolate Acetate and Derivatives.*—Methyl dihydromasticadienolate acetate (80 mg.) in " AnalaR " acetic acid (5 ml.) was hydrogenated over platinum for 2 hr. at room temperature. Crystallisation of the product from aqueous methanol furnished *methyl iso**dihydromasticadienolate acetate*, m. p. 97—98°, $[\alpha]_D$ −5° (*c* 1·10), $\lambda_{max.}$ 205 mμ (ε 5200) (Found : C, 76·9; H, 10·65%).

This methyl ester acetate (200 mg.) in " AnalaR " acetic acid (10 ml.) was treated at room temperature with chromium trioxide in the same solvent (0·5*N*; 10 ml.) for 3 days. The product was chromatographed over alumina, elution with benzene–light petroleum mixtures affording *methyl iso**dihydro*-7 : 11-*dioxomasticadienolate acetate*, m. p. 115—116° (from aqueous methanol), $[\alpha]_D$ −13° (*c* 1·06), $\lambda_{max.}$ 270 mμ (ε 8000) (Found : C, 73·25; H, 9·15. $C_{33}H_{50}O_6$ requires C, 73·05; H, 9·6%). Under the same oxidation conditions methyl dihydromasticadienolate acetate gave no ultraviolet chromophore.

The 7 : 11-diketone (50 mg.) in " AnalaR " acetic acid (2 ml.) was heated on the steam-bath with excess of zinc dust for 1 hr. Chromatography of the product over alumina in benzene–light petroleum mixtures gave the saturated 7 : 11-*diketone*, m. p. 177—179° (from methanol), $[\alpha]_D$ −117° (*c* 0·87), ε <200 at 220—320 mμ (Found : C, 72·4; H, 9·3. $C_{33}H_{52}O_4$ requires C, 72·75; H, 9·3%).

Hydrolysis of methyl *iso*dihydromasticadienolate acetate (100 mg.) with ethanolic potassium hydroxide (3%; 10 ml.) for 2 hr. under reflux gave iso*dihydromasticadienolic acid*, m. p. 210—212° (from aqueous methanol), $[\alpha]_D$ −6° (*c* 1·40) (Found : C, 78·7; H, 11·35. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%).

Dihydromasticadienediol and its Derivatives.—Methyl dihydromasticadienolate (650 mg.) in dry ether (150 ml.) was reduced with lithium aluminium hydride (380 mg.) in the same solvent under reflux for 2 hr. Crystallisation of the product from methanol furnished *dihydromasticadienediol*, m. p. 165—166°, $[\alpha]_D$ −55° (*c* 1·65) (Found : C, 81·4; H, 12·4. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). This diol can also be obtained conveniently by the analogous reduction of dihydromasticadienonic acid.

Dihydromasticadienediol (178 mg.) in pyridine (3 ml.) was treated with toluene-*p*-sulphonyl chloride (611 mg.) (initial cooling) for 30 min. at room temperature. The product was chromatographed over alumina (6 g.) in 1 : 1 benzene–light petroleum. Elution with this solvent (four fractions) gave an oil, the absorption spectrum of which ($\lambda_{max.}$ 225 mμ; ε 29,000) showed that it was the ditoluene-*p*-sulphonate. Elution with benzene (14 fractions) gave a crystalline product, m. p. approx. 100—104° (from aqueous methanol), $[\alpha]_D$ −35° (*c* 1·05), the absorption spectrum of which ($\lambda_{max.}$ 225 mμ; ε 14,300) indicated that it was the *monotoluene*-p-*sulphonate* (Found : C, 74·3; H, 9·35; S, 5·35. $C_{37}H_{58}O_4S$ requires C, 74·2; H, 9·75; S, 5·35%). Elution with 1 : 9 ether–benzene (three fractions) gave back unchanged starting material (m. p. and

mixed m. p.). Increasing the reaction time increased the ratio of di- to mono-toluene-*p*-sulphonate; after 4 hr. only the oily ditoluene-*p*-sulphonate could be isolated. Reduction of the mono- or of the di-toluene-*p*-sulphonate, or of the crude toluene-*p*-sulphonation mixture, with lithium aluminium hydride gave in each case the same result. The following experiment is exemplary. The monotoluene-*p*-sulphonate (91 mg.) in dry ether (25 ml.) was refluxed with lithium aluminium hydride (800 mg.) in the same solvent (25 ml.) for 36 hr. The product in benzene was chromatographed over alumina (3 g.). Elution with 1 : 19 ether–benzene (seven fractions) furnished *tirucall-7-enol*, m. p. 108—110° (from methanol), $[\alpha]_D$ −53° (*c* 1·05), $\lambda_{max.}$ 207 mμ (ε 4900) (Found : C, 84·05; H, 12·4. $C_{30}H_{52}O$ requires C, 84·05; H, 12·25%). Treatment with pyridine–acetic anhydride overnight at room temperature gave *tirucall-7-enyl acetate*, m. p. 127—128° (from chloroform–methanol), $[\alpha]_D$ −30° (*c* 1·46) (Found : C, 81·7; H, 11·85. $C_{32}H_{54}O_2$ requires C, 81·65; H, 11·55%). This acetate (160 mg.) in " AnalaR " acetic acid (26 ml.) was hydrogenated over platinum for 2 hr. The product, after crystallisation from chloroform–methanol, was identified as tirucallenyl acetate by m. p., mixed m. p., rotation {$[\alpha]_D$ −15° (*c* 0·98 in C_6H_6), −6° (*c* 1·08)}, and analysis (Found : C, 81·45; H, 11·3%). Alkaline hydrolysis (5% ethanolic potassium hydroxide on the steam-bath for 2 hr.) gave (from methanol) tirucallenol, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +2° (*c* 0·93 in C_6H_6), −11° (*c* 1·03)}, absorption spectrum (λ_{max} 205 mμ; ε 6700), and analysis (Found : C, 83·65; H, 12·2. Calc. for $C_{30}H_{52}O$: C, 84·05; H, 12·25%).

Masticadienediol (94 mg.) was acetylated with pyridine–acetic anhydride overnight at room temperature. The diacetate, which did not crystallise, was hydrogenated in " AnalaR " acetic acid (30 ml.) over platinum oxide for 14 hr. The product was hydrolysed with 5% ethanolic potassium hydroxide under reflux for 2 hr., to give iso*dihydromasticadienediol* (56 mg.), m. p. 157—158° (from methanol), $[\alpha]_D$ −5° (*c* 1·02) (Found : C, 80·9; H, 11·6. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Methyl iso*Dihydro-7-oxomasticadienolate Acetate.*—Methyl *iso*dihydromasticadienolate acetate (250 mg.) in ethyl acetate (10 ml.) was ozonised at −25° until a portion of the solution gave a negative test with tetranitromethane. The solution was washed with cold aqueous ferrous sulphate (5%), and the ethyl acetate removed *in vacuo*. The product was chromatographed over alumina (7·0 g.) in 1 : 3 light petroleum–benzene. Elution with benzene (four fractions) gave *methyl* iso*dihydro-7-oxomasticadienolate acetate* (20 mg.), m. p. 138—140° (from aqueous methanol), $[\alpha]_D$ −15° (*c* 1·35), $\lambda_{max.}$ 255 mμ (ε 10,000) (Found : C, 75·25; H, 9·75. $C_{33}H_{52}O_5$ requires C, 74·95; H, 9·9%). Methyl dehydrodihydromasticadienolate acetate (see above), ozonised under the same conditions, showed no sign of any enone chromophore in the ultraviolet spectrum and gave no tractable product on chromatography.

Rearrangement of Methyl Dihydromasticadienolate Acetate with Deuterium.—[*carboxy*-^{2}H]-Acetic acid was prepared by treating " AnalaR " acetic anhydride with the theoretical amount of deuterium oxide. The acid was purified by repeated fractional distillation, and its purity checked by titration. For the rearrangement standard conditions, the adequacy of which was checked by using ordinary hydrogen, were employed as follows. Methyl dihydromasticadienolate acetate (200 mg.) in deuteroacetic acid (17 ml.) was shaken for 3 hr. over platinum oxide (100 mg.) under 1 atm. of deuterium. The latter was prepared by the addition of deuterium oxide (6 ml.; mixed with dioxan, 5 ml.) to metallic sodium (3·0 g.; small pieces) suspended in dioxan (7 ml.). The dioxan was purified twice before use. The apparatus was of the vacuum type and the deuterium came into contact only with mercury. The product of rearrangement had the same physical constants as those recorded above for methyl *iso*dihydromasticadienolate acetate. In CCl_4 the compound showed an infrared band at 2100 cm.$^{-1}$ indicative of *C*-deuterium and of an intensity (band area; calibrated against 27-deutero-α-amyrin acetate of known deuterium content) equivalent to 1·13 *C*-D. This product was ozonised as described above, giving the 7-oxo-derivative, m. p. and mixed m. p. 137—140°, $[\alpha]_D$ −14° (*c* 0·92), $\lambda_{max.}$ 255 mμ (ε 10,000). Infrared examination as above showed 0·0 *C*-D.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance. One of us (E. S.) is indebted to the Consejo Superior de Investigaciones Cientificas (Spain), to the British Council, and to the University of Glasgow (I.C.I. Fellowship) for making this research possible. The authentic specimens of tirucallenol and its acetate were very kindly provided by Professor F. L. Warren (University of Natal).

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802. *Further Crystalline Constituents of Gum Mastic.*

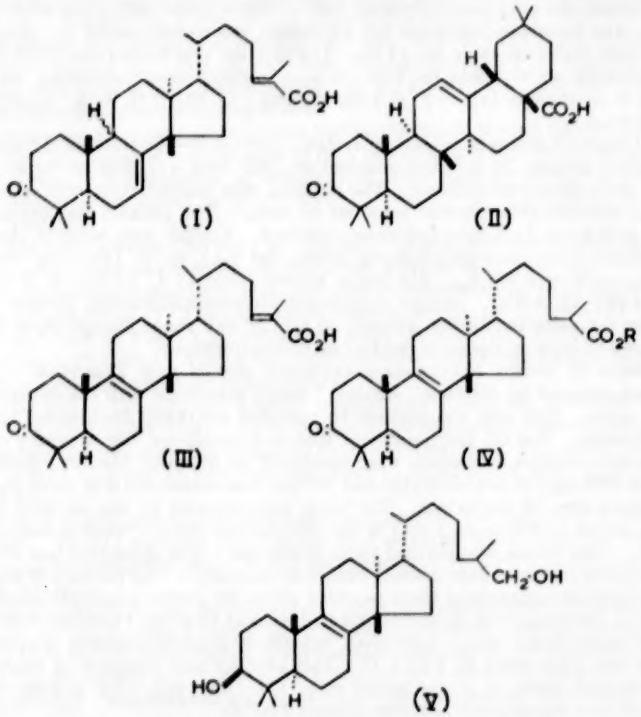
By Eliseo Seoane.

From the acid fraction of gum mastic oleanonic acid and a new triterpenoid keto-acid have been isolated. The latter acid has been related to masticadienonic acid from which it differs only in the position of one ethylenic linkage.

In a recent paper [1] an investigation of the constituents of gum mastic was reported. From the neutral fraction tirucallol was isolated, whilst from the acidic fraction a new triterpenoid acid, masticadienonic acid (I), was obtained. The present paper deals with two further crystalline constituents of the resin, both isolated from the acidic fraction.

As already briefly mentioned,[1] the portion of the acidic fraction soluble in dilute sodium hydroxide solution contains a crystalline acid. This has now been identified as oleanonic acid (II).

From the less strongly acidic fraction a new crystalline triterpenoid keto-acid, characterised as its methyl ester, has also been isolated. For reasons outlined below this is designated



*iso*masticadienonic acid and has the constitution and stereochemistry summarised in (III). This acid, $C_{30}H_{46}O_3$, was very similar in many respects to masticadienonic acid. Thus it contained, from its ultraviolet absorption spectrum, an $\alpha\beta$-unsaturated carboxylic acid function. Ozonolysis gave one mol. of acetic acid as with masticadienonic acid (I). The presence of the ketone grouping was indicated by a positive Zimmermann test,[2] by reduction with sodium borohydride to *iso*masticadienoloic acid, and by reduction with

[1] Barton and Seoane, preceding paper.
[2] Zimmermann, *Z. physiol. Chem.*, 1935, **233**, 257; 1936, **245**, 47; Barton and de Mayo, *J.*, 1954, 887.

lithium aluminium hydride to *iso*masticadienediol. As with masticadienonic acid,[1] hydrogenation over palladium proceeded smoothly with uptake of one mol. of hydrogen to furnish dihydro*iso*masticadienonic acid (IV; R = H), further characterised as the methyl ester (IV; R = Me). Reduction of this dihydro-acid (IV; R = H) with sodium borohydride afforded dihydro*iso*masticadienoloic acid whilst reduction with lithium aluminium hydride gave dihydro*iso*masticadienediol (V) identical with an authentic specimen [1] of established structure.

These facts enable one to deduce the correctness of formula (III) for *iso*masticadienonic acid and suggest [3] that mild acid treatment of masticadienonic acid should afford the new *iso*-acid. This was confirmed experimentally. In an analogous series of experiments methyl masticadienolate acetate was transformed into dihydro*iso*masticadienoloic acid identical with material prepared by the route indicated above.

Experimental

Rotations were determined in $CHCl_3$ solution. Ultraviolet absorption spectra were taken in EtOH solution with the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and his associates. Silica gel for chromatography was obtained from Messrs. Hopkin and Williams Ltd. Light petroleum of b. p. 40—60° was used throughout, unless stated to the contrary.

Isolation of Oleanonic Acid.—The acidic fraction (10 g.) extracted with 0·5N-sodium hydroxide in 5 : 1 light petroleum–benzene (200 ml.) was chromatographed over silica gel (400 g.), elution being with increasing proportions of benzene and then with 3 : 1 benzene–ether (25 fractions). Crystallisation of the material eluted with benzene from ether–light petroleum and from methanol gave oleanonic acid (2·5 g.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +101° (*c* 1·63)}, and analysis (Found: C, 79·05; H, 10·45. Calc. for $C_{30}H_{46}O_3$: C, 79·25; H, 10·2%). The identity was confirmed by conversion into the methyl ester {m. p., mixed m. p., and rotation, $[\alpha]_D$ +94° (*c* 1·26)} (Found: C, 79·3; H, 10·8. Calc. for $C_{31}H_{48}O_3$: C, 79·45; H, 10·3%) and into methyl oleanolate acetate.

Isolation of iso*Masticadienonic Acid.*—The mother-liquors from the crystallisation of masticadienonic acid (see Barton and Seoane [1]) gave on long storage further crystalline material (14 g. from about 800 g. of gum mastic). This material in benzene (150 ml.) was chromatographed over silica gel (600 g.), which was eluted with up to 1 : 9 ether–benzene (18 fractions of approx. m. p. 140—150° and $[\alpha]_D$ −11°). These fractions were combined and systematically triangulated from 1 : 3 ether–light petroleum. In this way the 14 g. of crystals were separated into pure masticadienonic acid (3·0 g.) and pure iso*masticadienonic acid* (1·12 g.). Recrystallised from the same solvent mixture, this had m. p. 166—167°, $[\alpha]_D$ +34° (*c* 1·10), $\lambda_{max.}$ 212 mμ (ε 15,000) (Found: C, 79·05; H, 9·9. $C_{30}H_{46}O_3$ requires C, 79·25; H, 10·2%). Treatment with diazomethane gave *methyl* iso*masticadienonate*, m. p. (from methanol) 111°, $[\alpha]_D$ +36° (*c* 1·05) (Found: C, 79·15; H, 10·0. $C_{31}H_{48}O_3$ requires C, 79·45; H, 10·3%). Ozonolysis of *iso*masticadienonic acid as described by Barton and Seoane [1] gave the same result (acetic acid identified as the *p*-bromophenacyl ester).

iso*Masticadienoloic Acid.*—*iso*Masticadienonic acid (200 mg.) in methanol (40 ml.) was treated with sodium borohydride (100 mg.) in the minimum of water at room temperature overnight. Crystallisation from methanol gave iso*masticadienoloic acid*, m. p. 171—172°, $[\alpha]_D$ −3° (*c* 1·14) (Found: C, 78·9, 78·8; H, 10·5, 10·65. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

iso*Masticadienediol.*—*iso*Masticadienonic acid (130 mg.) in dry ether (30 ml.) was refluxed overnight with lithium aluminium hydride (140 mg.) in the same solvent. Crystallisation from methanol gave iso*masticadienediol*, m. p. 157—158°, $[\alpha]_D$ −5° (*c* 1·02) (Found: C, 80·8; H, 11·1. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

Dihydroisomasticadienonic Acid.—*iso*Masticadienonic acid (400 mg.) in ethyl acetate (200 ml.) was hydrogenated over palladised charcoal as for masticadienonic acid.[1] Crystallisation from aqueous methanol afforded *dihydroisomasticadienonic acid*, m. p. 155—157°, $[\alpha]_D$ +27° (*c* 1·01) (Found: C, 79·35, 79·45; H, 10·5, 10·45. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). This acid was also obtained by acid-catalysed isomerisation of dihydromasticadienonic acid by the procedure detailed below. Treatment with diazomethane in the usual way afforded *methyl dihydro*iso*masticadienonate*, m. p. 75—77°, $[\alpha]_D$ +26° (Found: C, 79·05; H, 10·1. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%).

[3] Cf. Irvine, Lawrie, McNab, and Spring, *Chem. and Ind.*, 1955, 626; Dawson, Halsall, Jones, Meakins, and Phillips, *ibid.*, p. 918.

Dihydroisomasticadienoloic Acid.—Dihydro*iso*masticadienonic acid (124 mg.) in methanol (20 ml.) was treated with sodium borohydride (excess) in the minimum of water and left overnight. Crystallisation from aqueous methanol furnished *dihydroisomasticadienoloic acid*, m. p. 210—213°, $[\alpha]_D$ −6° (*c* 1·00) (Found: C, 78·65, 78·75; H, 10·8, 10·8. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%).

Dihydroisomasticadienediol.—Dihydro*iso*masticadienonic acid (400 mg.) in dry ether (50 ml.) was treated with lithium aluminium hydride (300 mg.) in the same solvent under reflux overnight. Chromatography of the product over silica gel (20 g.) and elution with benzene and with 1 : 4 ether–benzene gave dihydro*iso*masticadienediol identical {m. p., mixed m. p., rotation, $[\alpha]_D$ +3° (*c* 1·75)} with material described in the earlier paper as "*iso*dihydromasticadienediol."

Isomerisation of Masticadienonic Acid.—The acid (103 mg.) in chloroform (10 ml.) was treated at 0° with dry hydrogen chloride for 2 hr. Crystallisation of the product from ether–light petroleum gave masticadienonic acid, identified by m. p., mixed m. p., rotation, and infrared spectrum.

In a similar correlation methyl masticadienolate acetate (100 mg.) in chloroform (10 ml.) was isomerised in the same way. The product was hydrolysed with 5% ethanolic potassium hydroxide. Crystallisation from methanol gave dihydro*iso*masticadienoloic acid (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −6° (*c* 1·40)}.

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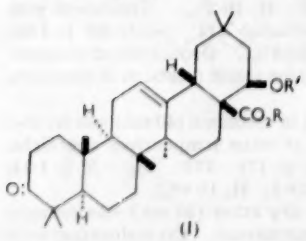
803. *Triterpenoids. Part XXIII.* The Nature of Lantadene A.*

By D. H. R. BARTON, P. DE MAYO, and J. C. ORR.

Lantadene A has again been isolated from *Lantana camara*. By a comparison of purified lantadene A and its derivatives with rehmannic acid and its corresponding derivatives their identity has been established. This conclusion has been confirmed by degradation.

IN a previous Part [1] of this series the constitution of lantadene B was established as (I; R = H, R′ = ββ-dimethylacryloyloxy). The more interesting, physiologically active lantadene A, isolated and studied by Louw,[2] has not hitherto been available to us for investigation. From a specimen of *Lantana camara* of Australian origin, we have recently been able to isolate again lantadene A. The present paper is our report on its constitution.



(I)

Louw [2] stated that lantadene A formed a methyl ester, a 2 : 4-dinitrophenylhydrazone, and an acetate. For convenience of exposition the physical constants found by Louw [2] are summarised in the Table. The lantadene A isolated in our own work had constants also as summarised in this Table in reasonable agreement with those of Louw. Through the courtesy of Dr. O. Jeger (Zürich) in forwarding to us small authentic specimens of lantadene A and its 2 : 4-dinitrophenylhydrazone, obtained originally from Dr. P. G. J. Louw, we have been able to confirm the authenticity of our material. By the criteria summarised in the Experimental section the homogeneity of lantadene A, as now described, was established. The identity of lantadene A with rehmannic acid [3] (I; R = H, R′ = angeloyloxy), first suggested by the physical constants

* Part XXII, *J.*, 1956, 4150.

[1] Barton, de Mayo, Warnhoff, Jeger, and Perold, *J.*, 1954, 3689.

[2] Louw, *Onderstepoort J. Vet. Sci.*, 1943, **18**, 197; 1948, **23**, 233; 1949, **22**, 321, 329; see also Sanders, *J. Amer. Vet. Med. Assoc.*, 1946, 139.

[3] Barton and de Mayo, *J.*, 1954, 887, 900.

summarised in the Table, was confirmed by all the usual criteria. However, in view of the importance of lantadene A and the fact that m. p. depressions are not always observed [1] in such closely related compounds, we deemed it advisable to repeat on lantadene A the degradation previously applied [3] to rehmannic acid. The identical

	Lantadene A (authentic) [2]		Lantadene A (this paper)		Rehmannic acid [3]		Lantadene B [1]	
	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$
Acid	276—280° 282—287° *	+81°	282—286°	+89°	282—287°	+84°	293—294°	+85°
Me ester	125	—	137—139	+86	140	+86	234—236	+89
2 : 4-Dinitrophenylhydrazone	268	+35	271—272	+35	273—274	+27	264—265	+48

* After several recrystallisations.

results obtained confirm beyond question that lantadene A and rehmannic acid are the same compound. The acetate [2] of lantadene A must, of course, be a mixed anhydride of the same type that we prepared earlier [1] from lantadene B.

Our experiences with *Lantana camara* have shown that this plant is very variable in its triterpenoid content. Material examined previously [1] contained only lantadene B. The Queensland *L. camara*, from which we isolated lantadene A, had only traces of lantadene B. A specimen of South African origin, which recently came to hand, contained no crystallisable triterpenoid material.

Now that the constitutions of the (indirectly) photosensitising triterpenoids icterogenin [3,4] and lantadene A (rehmannic acid) have been elucidated, the way is clear for studies on the relation between physiological activity and molecular structure.

Experimental

For general experimental conditions see Part VII.[4] Rotations were determined in $CHCl_3$ solution. Ultraviolet absorption spectra were taken in EtOH solution with the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and his associates. Silica gel for chromatography was obtained from Messrs. Hopkin and Williams Ltd. Light petroleum of b. p. 40—60° was used throughout unless stated to the contrary. The m. p.s of lantane A and rehmannic acid were determined as follows: the sample was inserted at 220° and heated at about one degree per 3·5 sec. to 260° and then at one degree per 15 sec. until melted.

Examination of Australian Lantana camara.—The material examined (C.S.I.R.O. sample number 5384) was worked up essentially according to the directions of Louw.[2] The powdered leaves and terminal branchlets (1·7 kg.) were extracted with methanol (7 l.) at room temperature (occasional stirring) for 2 days. The green solution was filtered and concentrated *in vacuo* to 3 l. Chlorophyll was removed by stirring with charcoal (3 × 25 g.), and the resultant brown solution evaporated to dryness, on a steam-bath, *in vacuo*. The residue was dissolved in hot methanol (200 ml.), diluted with benzene (1·5 l.), and left for 2 days at room temperature. The benzene solution was decanted from precipitated tar (water-soluble glycosides), and evaporated to dryness, on a steam-bath, *in vacuo*. Benzene (3 × 100 ml.) was added and removed in the same way to ensure that no methanol remained. The residue was taken up in benzene (200 ml.) and chromatographed over silica gel (230 g.). Elution with benzene–ether with proportions of ether increasing up to 100% gave 13 fractions of crystalline (from benzene or methanol) material with m. p.s ranging from 224—244° to 267—270°. The highest-melting fractions were combined and recrystallised from chloroform–methanol to constant m. p., to furnish *lantadene A* (prisms; 1·5 g.), m. p. 282—286°, $[\alpha]_D$ + 89° (*c* 1·41), $\lambda_{max.}$ 209 and 280 mμ (ε 13,900 and 130 respectively) (Found: C, 75·9; H, 9·45. $C_{35}H_{52}O_5$ requires C, 76·05; H, 9·5%). The homogeneity of this material was established by extensive crystallisation and by further chromatography over silica gel. Lantadene A crystallises in two forms, prisms (see above) and needles. The two forms have identical physical constants and can be interconverted by seeding.

Lantadene A was undepressed on admixture with authentic lantadene A, m. p. 276—280°, provided by Dr. Louw, and with rehmannic acid, m. p. 282—287°. The higher m. p. (295—300°)

[4] Rimington, Quin, and Roets, *Onderstepoort J. Vet. Sci.*, 1937, **9**, 225.
[3] Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339.

recorded for the last substance earlier [3] refers to insertion at 260° and rapid heating. Since the m. p.s vary so much it is recommended that all comparative m. p.s should be taken simultaneously. Lantadene A was, however, slightly depressed in m. p. on admixture with lantadene B. Authentic lantadene A, lantadene A as described in the present paper, and rehmannic acid, all had identical infrared spectra in Nujol.

Methylation with diazomethane gave *lantadene A methyl ester*, m. p. (solvated needles from methanol) 137—139°, $[\alpha]_D$ + 86° (*c* 2·15) (Found: C, 75·7; H, 10·15. $C_{34}H_{54}O_5.\frac{1}{2}CH_4O$ requires C, 75·25; H, 9·7%). A non-solvated form, m. p. 149—150°, was obtained by crystallisation from benzene–light petroleum; further recrystallisation from methanol gave the solvated form.

In order to confirm the homogeneity of lantadene A, material (m. p. 280—282°) (256 mg.) was methylated with diazomethane and chromatographed over alumina (20 g.) in light petroleum. Elution with light petroleum–benzene mixtures up to 100% benzene content (19 fractions) gave only lantadene A methyl ester. Elution with 1 : 9 ether–benzene furnished lantadene B methyl ester (m. p. and mixed m. p.; 3 mg.). Lantadene A methyl ester was undepressed in m. p. (solvated form) on admixture with methyl rehmannate.

Lantadene A was converted into its 2 : 4-dinitrophenylhydrazone in the usual way. Recrystallised from methanol this had m. p. 271—272°, $[\alpha]_D$ + 35° (*c* 1·07) (Found: C, 67·45; H, 7·55; N, 7·3. Calc. for $C_{41}H_{58}O_8N_4$: C, 67·2; H, 7·7; N, 7·65%). It was undepressed in m. p. on admixture with authentic material, m. p. 268°, $[\alpha]_D$ + 35° (*c* 0·23), from Dr. Louw and with rehmannic acid 2 : 4-dinitrophenylhydrazone, m. p. 273—274°, $[\alpha]_D$ + 27° (*c* 0·34). The authentic 2 : 4-dinitrophenylhydrazone, that from lantadene A as described in the present paper, and the corresponding rehmannic acid derivative, had identical infrared spectra in Nujol. Lantadene B 2 : 4-dinitrophenylhydrazone [1] had $[\alpha]_D$ + 48° (*c* 0·42).

Pyrolysis of Lantadene A Methyl Ester.—The methyl ester (89·2 mg.) was pyrolysed at 530°/0·15 mm. under the conditions used by Barton and de Mayo.[3] The acid eliminated (0·87 mol.) was identified as angelic acid by m. p. and mixed m. p. (liquefied on admixture with tiglic acid). The neutral portion of the pyrolysate was chromatographed over alumina (4 g.) in light petroleum. Elution with 1 : 1 benzene–light petroleum gave oils (46·4 mg.). Elution with benzene afforded unchanged lantadene A methyl ester (m. p. and mixed m. p.). The oily fractions, on hydrogenation in " AnalaR " acetic acid over platinum for 20 hr. (uptake, 2 mols. of hydrogen), and acetylation with pyridine–acetic anhydride overnight at room temperature, gave methyl oleanolate acetate (m. p., mixed m. p., and rotation). The identity was confirmed by alkaline hydrolysis to methyl oleanolate (m. p., mixed m. p., and rotation) and by benzoylation (pyridine–benzoyl chloride overnight at room temperature) to methyl oleanolate benzoate (m. p., mixed m. p., and rotation).

Hydrolysis of Lantadene A.—Lantadene A (127 mg.) was refluxed for 8 hr. with ethanolic potassium hydroxide (4%; 10 ml.). Chromatography of the product over silica gel (5 g.) in 1 : 1 benzene–light petroleum (b. p. 60—80°) gave (13 fractions), on elution with 1 : 1 benzene–ether, 22β-hydroxyoleanonic acid (m. p. and mixed m. p.). The identity was confirmed by methylation to give methyl 22β-hydroxyoleanonate (m. p., mixed m. p., and rotation).

Examination of South African Lantana camara.—The powdered leaves and branchlets (1·52 kg.) were extracted and processed as described above. However, even repeated chromatography afforded no crystalline ketonic (to the Zimmermann reagent) fraction.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance. Australian *Lantana camara* (from Queensland) was kindly provided by the C.S.I.R.O. through the courtesy of Dr. J. R. Price, to whom we express our best thanks. We are also most grateful to the Chief of the Division of Botany, Dept. of Agriculture of the Union of South Africa, Pretoria, South Africa, for a supply of South African material. Part of this work was carried out whilst one of us (J. C. O.) was in receipt of a D.S.I.R. Maintenance Grant.

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804. *The Constituents of* Casimiroa edulis *Llave* et *Lex. Part I. The Seed.**

By F. A. Kincl, J. Romo, G. Rosenkranz, and Franz Sondheimer.

The seeds of the Mexican tree *Casimiroa edulis* Llave *et* Lex. contain seven substances in addition to the previously isolated casimiroin, casimiroedine, casimirolid, a " yellow phenolic substance " (identified as 9-hydroxy-4-methoxyfurano[3,2-*g*]benzopyran-7-one) (II; R = OH), β-sitosterol β-D-glucoside, and β-sitosterol. Of these seven, two were identified as palmitamide and *N*-benzoyltyramine, whereas the other five appear to be new.

Casimiroa edulis Llave *et* Lex. (Rutaceae) is a tree growing in the temperate region of Mexico and Central America. The fruit, known as " Zapote blanco " (literally " the white fruit "), is commonly eaten in Mexico and has a pleasant flavour. Since Francisco Hernandez [1] claimed the fruit to induce sleep and the kernels to be a powerful poison, a variety of physiological actions have been attributed to the plant. The literature up to 1911 has been adequately reviewed by Power and Callan [2] who carried out the only extensive previous chemical investigation of these seeds and found no foundation for the reported physiological activities.

However, reports regarding the hypnotic, sedative, and hypotensive action of the seed persisted.[3] We now report a chemical re-investigation of the alcohol-soluble constituents of the seed. A study of the bark is reported in the following paper.

Power and Callan [2] isolated six substances from the fruit, namely, casimiroin ($C_{24}H_{20}O_8N_2$), casimiroedine ($C_{17}H_{24}O_5N_2$), casimirolid ($C_{24}H_{28}O_6$), a " yellow phenolic substance " ($C_{16}H_{12}O_6$), β-sitosterol β-D-glucoside (at the time called " ipuranol " and identified later [4]), and β-sitosterol.† We have been able to obtain all of these, but of the new compounds could confirm the empirical formula only of casimiroedine. In addition, we have found seven further compounds, of which five (zapotin, zapotinin, zapoterin, eduline, and zapotidine) appear to be new and two (palmitamide and *N*-benzoyltyramine) are known. In view of the extensively described physiological action of tyramine (one of the active principles of ergot), the *N*-benzoyl derivative of this substance is probably responsible for some of the ascribed activity of the seed.

The separation procedure employed consisted in evaporating the alcoholic extract of the kernels, adding dilute hydrochloric acid and extracting the mixture successively with solvents of increasing polarity, whereby " acid " extracts were obtained. The remaining aqueous layer was then basified with ammonia and again treated with the same solvents to give " alkaline " extracts. The material from each solution was chromatographed unless it crystallised directly. The results are summarised in the Table.

The " acid " hexane extract on chromatography on alumina yielded successively β-sitosterol and palmitamide each of which was identified by comparison with an authentic specimen. Although β-sitosterol has been isolated previously from many different natural sources, this appears to be the first case of palmitamide's being found in the plant kingdom.

Chromatography of the " acid " benzene extract led to zapotin, casimiroin, and *N*-benzoyltyramine. Zapotin, $C_{19}H_{18}O_6$, formed a picrate, perchlorate, and oxime; it contains four methoxyl groups which, combined with the ultraviolet absorption data and general colour reactions, indicated that it was a tetramethoxy-flavone or -*iso*flavone. The close similarity of the infrared spectra in the carbonyl region between zapotin (6·03, 6·22,

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† In addition, benzoic acid and a mixture of fatty acids were obtained. Bickern (*Arch. Pharm.*, 1903, **241**, 166) isolated two other compounds, the " gluco-alkaloid " casimirin and casimirol, that were obtained neither by Power and Callan nor by ourselves.

[1] Hernandez " Rerum medicarum Novae Hispaniae thesaurus, etc.," Rome, 1651, Lib. III, p. 89.

[2] Power and Callan, *J.*, 1911, **99**, 1993.

[3] *Inter al.*, de Lille, *Anales inst. biol.* (*Mex.*), 1934, **5**, 45; Mendez, *J. Amer. Inst. Homeopathy*, 1937, **30**, 271; Ramirez and Rivero, *Rev. mensual med. Mexico*, 1936, **9**, I, No. 3; *Farmacopea Mexicana*, 6th edn., 1952, p. 423.

[4] Power and Salway, *J.*, 1913, **399**.

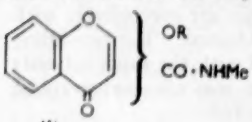
and 6·28 μ) and 5 : 6-dimethoxyflavone (6·03, 6·18, and 6·29 μ; see following paper) supports this formulation. With hydrogen iodide zapotin gave the tetrahydroxy-compound demethylzapotin, which on fusion with potassium hydroxide yielded salicylic acid and, as sole phenol, resorcinol (rather than the expected tri- or tetra-hydroxybenzene). Furtherwork is being carried out to elucidate the structure of zapotin, which appears to differ from the known tetramethoxy-flavones and *-iso*flavones.

We consider our casimiroin to be identical with that of Power and Callan [2] in view of the similar properties of the bases and their aurichlorides and particularly since short treatment with hydrochloric acid gives an acid, m. p. 321—323° (reported: [2] m. p. >300°), which we name casimiroinol. Analysis of casimiroin points to the formula

Compound	Extraction solvent	Yield (%)
β-Sitosterol	" Acid " hexane	0·0027
Palmitamide	,,	0·0003
Zapotin	,, benzene	0·004
Casimiroin (I; R = Me)	,,	0·0012
N-Benzoyltyramine	,,	0·0015
Furanocoumarin (II; R = OH)	,, methylene chloride	0·0112
Zapotinin	,,	0·0005
Zapoterin	,,	0·0027
Casimirolid	,,	0·0021
Sitosterol β-D-glucoside	,, pentyl alcohol	0·0016
Eduline	" Alkaline " benzene	0·0002
Zapotidine	,, methylene chloride	0·0014
Casimiroedine	,, pentyl alcohol	0·95

$C_{12}H_{11}O_4N$ rather than $C_{24}H_{20}O_8N_2$ proposed by Power and Callan.[2] On the basis of our formula, casimiroin contains one methoxyl and one *N*-methyl group and forms a monopicrate, but the aurichloride contains 2 mols. of casimiroin and one of aurichloric acid. It was apparently because of the last salt that the C_{24} formula was favoured previously, since this requires the usual 1 : 1 aurichloride; direct molecular-weight determination of casimiroin points to the $C_{12}H_{11}O_4N$ formula. It has recently been shown [5] that salts of monosubstituted amides and hydrohalic acids may be formed in a 2 : 1 ratio and an elegant explanation was given: the same type of salt formation takes place between casimiroin and chloroauric acid.

Casimiroin was non-basic on titration with perchloric acid and this, combined with the infrared characteristics (see below), indicates an amide group. These facts suggest that the substance may be the methylamide of a methoxycoumarin-carboxylic or of a methoxychromonecarboxylic acid (cf. I; R = Me). Coumarins show an infrared band at *ca.* 5·80 μ [cf. the furanocoumarin (II; R = OH) and scopoletin (following paper)] due to the six-membered lactone grouping and the absence of this band in casimiroin rules out the coumarin structure. On the other hand, the striking similarity in the carbonyl region between 5 : 6-dimethoxyflavone (6·03, 6·18, and 6·29 μ; see following paper) and casimiroin (6·04, 6·12, 6·20, and 6·27 μ) strongly supports the chromone formulation (I; R = Me), the extra band at 6·12 μ being ascribed to the amide function.



(I)

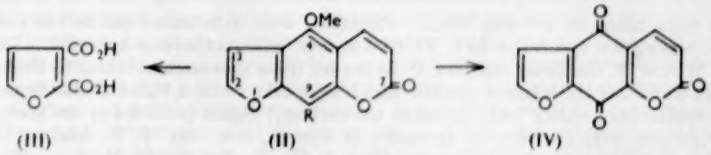
Casimiroinol has the formula $C_{11}H_9O_4N$. It is acidic (though showing no carboxyl function in the infrared spectrum) and contains no methoxyl group. Apparently it is related to casimiroin as a phenol to a methyl ether and accordingly treatment with diazomethane regenerated casimiroin.

The last compound to be eluted from the " acid " benzene extract had the formula $C_{15}H_{15}O_2N$. Ultraviolet absorption maxima at 226 (log ε 4·27) and 273 mμ (log ε 3·37) were due to a benzoate and a phenol group, respectively, as shown by the production of benzoic acid on alkaline fusion and disappearance of the 273 mμ band on acetylation. Methylation and subsequent oxidation furnished *p*-methoxybenzoic acid and the phenol was therefore *para*-substituted. The substance appeared to be *N*-benzoyltyramine (*N*-benzoyl-*p*-hydroxyphenethylamine), previously made by partial benzoylation of

[5] White, *J. Amer. Chem. Soc.*, 1955, **77**, 6215.

tyramine.[6] This was confirmed by preparation of the dibenzoyl derivative, which was identical with an authentic sample. Free tyramine, the decarboxylation product of tyrosine, has been found in ergot, mistletoe, and thistle.

The " acid " methylene chloride extract on direct crystallisation produced a yellow acidic substance, $C_{12}H_8O_5$, m. p. 223—224°, containing one methoxyl group. It is probably identical with the " yellow phenolic substance," m. p. 215—218°, of Power and Callan,[2] although these workers proposed the formula $C_{16}H_{12}O_6$. The presence of a hydroxyl function was shown by the formation of a monoacetate and a monobenzoate. Potassium permanganate oxidised it to furan-2 : 3-dicarboxylic acid (III), whereas chromium trioxide led to an orange product, $C_{11}H_4O_5$, containing no methoxyl group, which, it was suspected, was bergaptenquinone (IV).[7-9] The yellow substance, m. p. 223—224°, would then be 9-hydroxy-4-methoxyfurano[3,2-*g*]benzopyran-7-one (II; R = OH), obtained previously (m. p. 221°) from 4-aminobergapten (II; R = NH_2) by treatment with nitrous acid [10] and from byak-angelicin (II; R = $C_5H_{11}O_3$) [8] and phellopterin (II; R = C_5H_9O) [9] by acetic



(III) (II) (IV)

acid–sulphuric acid. Confirmation was provided by the methylation of our furanocoumarin with diazomethane to the dimethyl ether, *iso*pimpinellin (II; R = OMe).[11] The alternative (unknown) 9-hydroxy-4-methoxy-formulation is unlikely in view of the good agreement of the physical properties of our substance and of its acetate with those reported [9] for the compound (II; R = OH). A number of 4- and/or 9-substituted furanocoumarins (II) have been found in Nature, but the 4-hydroxy-9-methoxy-compound (II; R = OH) has previously been obtained only by the aforementioned conversions.

The " acid " methylene chloride extract, from which the yellow furanocoumarin (II; R = OH) had been removed, was chromatographed and thereby yielded successively zapotinin, zapoterin, and casimirolid. The first of these, zapotinin, was a yellow substance, $C_{18}H_{16}O_6$, m. p. 223—225°, containing one hydroxyl group (monoacetate) and three methoxyl groups. The formal relation with zapotin ($C_{19}H_{18}O_6$; no hydroxyl and four methoxyl groups) was at once apparent. In fact, zapotinin was obtained from zapotin by treatment with potassium hydroxide and from demethylzapotin by diazomethane. Therefore zapotinin is a trimethyl ether of the tetrahydroxy-flavone or -*iso*flavone of which zapotin is the tetramethyl ether.

Zapoterin, $C_{19}H_{24}O_6$, had no high-intensity ultraviolet absorption, whereas the infrared spectrum showed several bands in the carbonyl region. On attempted acetylation no acetyl groups were introduced, but an isomer, *iso*zapoterin, was formed.

The last substance to be eluted from the chromatogram of the " acid " methylene chloride extract had m. p. 229—231°, $[\alpha]_D$ −49°, and is therefore almost certainly identical with Power and Callan's casimirolid [2] (m. p. 229—230°, $[\alpha]_D$ −49°). Analysis of our casimirolid, however, indicated the formula $C_{28}H_{32}O_8$ and not $C_{24}H_{28}O_6$ as proposed by the British workers. The relation between casimirolid and obacunone,[12] and the formula of the latter, will be discussed in a later paper.

The " acid " pentyl alcohol extract crystallised directly and yielded β-sitosterol β-D-glucoside, further characterised as the tetra-acetate.

[6] Barger, *J.*, 1909, **95**, 1123.
[7] Thomas and Baetcke, *Ber.*, 1912, **45**, 3705.
[8] Noguchi (Noguti) and Kawanami, *ibid.*, 1938, **71**, 344.
[9] *Idem, J. Pharm. Soc. Japan*, 1940, **60**, 57.
[10] *Idem, Ber.*, 1938, **71**, 1428.
[11] *Inter al.*, Wessely and Kallab, *Monatsh.*, 1932, **59**, 161; Caldwell and Jones, *J.*, 1945, 540.
[12] Kaku and Ri, *J. Pharm. Soc. Japan*, 1935, **55**, 222; Emerson, *J. Amer. Chem. Soc.*, 1951, **73**, 2621.

The " alkaline " benzene extract on chromatography yielded eduline, m. p. 187—188°, a new alkaloid. Eduline has the composition $C_{17}H_{15}O_2N$, contains one methoxyl group, and forms a monopicrate and a monoperchlorate.

The " alkaline " methylene chloride extract produced a substance, $C_7H_9N_3S$, which we have named zapotidine. It contains one *N*-methyl group. When it is boiled with aqueous potassium hydroxide, acidification gives hydrogen sulphide and a basic liquid base with a smell reminiscent of pyridine. Zapotidine therefore appears to be a methyl-pyridyl-thiourea.

Finally, the " alkaline " pentyl alcohol extract furnished Power and Callan's casimiroedine,[2] $C_{17}H_{24}O_5N_2$, the constitution of which is being investigated by Professor Carl Djerassi.

Work is continuing on the substances for which we have suggested partial structures.

Experimental

M. p.s were taken on a Kofler block. Rotations were determined (at 20°) in $CHCl_3$, and ultraviolet absorption spectra in 95% EtOH solution, unless otherwise specified. Thanks are offered to Miss M. T. Cardenas and Mrs. P. Lopez for these measurements and to Professor Carl Djerassi for providing the infrared spectra, which were taken with a Baird double-beam infrared recording spectrophotometer [only bands in the carbonyl region (5·5—6·4 μ) are given; (w) = weak]. Analyses were by Mrs. A. Gonzalez of Syntex, S.A., Mr. J. F. Alicino, Metuchen, N. J., Drs. G. Weiler and F. B. Strauss, Oxford, Dr. A. Bernhardt, Mülheim (Ruhr), and Dr. R. Dietrich, Zürich. Molecular weights were determined by the Rast method, and neutral equivalent determinations by perchloric acid titration.

General Extraction Procedure.—The fruit of *Casimiroa edulis* Llave *et* Lex. was collected in the State of Hidalgo, Mexico, during March. The fleshy pulp was separated from the kernels and the latter were dried in the sun. The dried kernels (100 kg.) were coarsely ground and extracted twice with hot ethanol (2 × 400 l.). The combined alcoholic extracts were evaporated and the resulting dark brown syrup was diluted with 4% hydrochloric acid (50 l.). The mixture was extracted successively with hexane, benzene, methylene chloride, and pentyl alcohol (5 × 10 l. each), to give the " acid " extracts.

The residual aqueous phase was made alkaline with concentrated aqueous ammonia, with ice-cooling, then extracted with benzene, methylene chloride, and pentyl alcohol (5 × 10 l. each), giving the " alkaline " extracts.

Each of the extracts was evaporated and the residue (1 part) was chromatographed on alumina (*ca.* 40 parts) in the usual way. Results are given in the Table.

β-Sitosterol.—β-Sitosterol was obtained from the " acid " hexane extract and was eluted from the column with benzene–ether (7 : 3). It formed plates (from methanol), m. p. 138—139°, $[\alpha]_D$ −38° (lit.,[13] m. p. 140°, $[\alpha]_D$ −37°). The m. p. was undepressed on admixture with an authentic sample and the infrared spectra were identical. The acetate had m. p. 127—128°, $[\alpha]_D$ −38° (Found: C, 81·45; H, 11·45. Calc. for $C_{31}H_{52}O_2$: C, 81·5; 11·5%) (lit.,[13] m. p. 127—128°, $[\alpha]_D$ −41°). The benzoate had m. p. 145—147°, $[\alpha]_D$ −12° (lit.,[13]: m. p. 146—147°, $[\alpha]_D$ −14° [13]).

Palmitamide.—This was obtained from the " acid " hexane extract, and was eluted from the column with benzene–ether (1 : 1). It crystallised from methanol as plates, m. p. 103—104° (Found: C, 75·15; H, 12·95; N, 5·5%; *M*, 224. Calc. for $C_{16}H_{33}ON$: C, 75·25; H, 13·0; N, 5·5%; *M*, 255). Identity with an authentic sample (prepared from palmitoyl chloride and ammonia), m. p. 104°, was established by a mixed m. p. determination and infrared comparison.

Zapotin.—The first substance obtained by chromatography of the " acid " benzene extract was *zapotin*, eluted with benzene–ether (4 : 1). It separated from methanol or acetone as colourless prisms, m. p. 150—151°, $\lambda_{max.}$ 230, 255, and 324 mμ (log ε 4·45, 4·20, and 3·83, respectively), $\lambda_{max.}$ (in $CHCl_3$) 6·03, 6·22, and 6·28 μ (w) (Found: C, 66·65; H, 5·45; OMe, 36·8%; *M*, 340. $C_{19}H_{18}O_6$ requires C, 66·65; H, 5·3; 4OMe, 36·25%; *M*, 342), and gave positive Wilson and Shinoda colour reactions for flavonoids and with concentrated sulphuric acid an intense yellow colour. The *picrate* formed yellow needles (from methanol), m. p. 181—182° (Found: C, 52·2; H, 3·9; N, 7·05. $C_{19}H_{18}O_6.C_6H_3O_7N_3$ requires C, 52·55; H, 3·7; N, 7·35%). The *perchlorate*, prepared in acetone, crystallised from acetone–ether as yellow needles,

[13] Elsevier, " Encyclopaedia of Organic Chemistry," 1940, Vol. XIV, p. 90.

m. p. 204—206° (Found: C, 51·2; H, 4·55; Cl, 8·2. $C_{19}H_{18}O_6,HClO_4$ requires C, 51·55; H, 4·3; Cl, 8·0%). The *oxime*, prepared in boiling methanol–pyridine for 2 hr., separated from ethyl acetate–ether as light yellow crystals, m. p. 240—243° (Found: C, 64·3; H, 5·25; N, 4·25. $C_{19}H_{19}O_6N$ requires C, 63·85; H, 5·35; N, 3·9%).

Demethylzapotin.—Zapotin (4 g.) in acetic anhydride (60 c.c.) and hydriodic acid (85 c.c.; *d* 1·7) was boiled under reflux for 1 hr. The cooled mixture was poured into ice and water, and the precipitate was washed with water and dried. This material (3·1 g.; m. p. 246—252°) on three successive sublimations in a high vacuum, yielded *demethylzapotin* as yellow needles, m. p. 321—325°, $\lambda_{max.}$ (mull) 5·96, 6·08, and 6·21 μ (Found: C, 63·2; H, 3·5; OMe, 0·0. $C_{18}H_{16}O_6$ requires C, 62·95; H, 3·5%). The substance gave a strong green colour with alcoholic ferric chloride.

Salicylic Acid and Resorcinol by Alkali-fusion of Demethylzapotin.—Powdered demethylzapotin (1 g.) was added gradualiy to potassium hydroxide (10 g.) and water (1 c.c.) at 130°. The temperature was increased to 170° during the next 30 min. and more potassium hydroxide (2 g.) was added. The temperature was raised to 210° during 15 min. and kept thereat for 10 min. The brown melt was allowed to cool, dissolved in water, and acidified with hydrochloric acid. The products were extracted with ether (*A*) and the organic extract was washed with sodium hydrogen carbonate solution. The aqueous layer was acidified and extracted with ether and this ether solution on drying, evaporation, and crystallisation from water produced salicylic acid (0·25 g.), m. p. and mixed m. p. 156—158° (identical infrared spectra).

The ether extract (*A*) was dried and evaporated. The resulting oil (0·22 g.), on benzoylation (Schotten–Baumann), yielded resorcinol dibenzoate (0·11 g.), m. p. and mixed m. p. 116·5° (from ethanol) (Found: C, 75·3; H, 4·7; O, 20·1. Calc. for $C_{20}H_{14}O_4$: C, 75·45; H, 4·45; O, 20·1%).

Casimiroin (I; R = Me).—*Casimiroin* was the second substance obtained by chromatography of the " acid " benzene extract and was eluted from the column with benzene–ether (3 : 1). It separated from methanol as feathery needles, m. p. 199—200°. Sublimation in a high vacuum yielded a sample, m. p. 202—203°, $\lambda_{max.}$ 226, 236, 252, 260, and 300 mμ (log ε 4·50, 4·45, 4·35, 4·34, and 3·84, respectively), $\lambda_{max.}$ (mull) 6·04, 6·12, 6·20, and 6·27 μ (Found: C, 61·8, 61·7; H, 4·7, 4·75; O, 27·55; N, 6·0; OMe, 13·4; *N*-Me, 6·1; *C*-Me, 0·0%; *M*, 214, 217. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·75; O, 27·45; N, 6·0; 1OMe, 13·3; 1*N*-Me, 6·45%; *M*, 233) (Power and Callan [3] give m. p. 196—197°). Casimiroin gave an intense orange colour with tetranitromethane and a red-brown colour with concentrated nitric acid. It was recovered unchanged from acetic anhydride–pyridine at 90°. Casimiroin *picrate* crystallised from methanol as yellow needles, m. p. 193—194° (Found: C, 46·75; H, 3·35. $C_{12}H_{11}O_4N,C_6H_3O_7N_3$ requires C, 46·75; H, 3·05%) (Power and Callan [3] give m. p. 165°). Casimiroin *aurichloride*, prepared in aqueous ethanol, formed pale orange needles (from methanol), m. p. 196—198° [Found: C, 35·4, 35·65; H, 3·0, 3·1; N, 3·45; Au, 24·45; Cl, 17·65. $(C_{12}H_{11}O_4N)_2,HAuCl_4$ requires C, 35·75; H, 2·85; N, 3·45; Au, 24·45; Cl, 17·6%] (Power and Callan [3] give m. p. 195—196°).

Casimiroinol (I; R = H).—Casimiroin (0·3 g.) was boiled under reflux with 20% hydrochloric acid (15 c.c.). The compound dissolved, but after 20 min. a copious precipitate had separated. The mixture was cooled, and the solid washed with water and dried. Crystallisation from methanol–chloroform produced *casimiroinol* (0·26 g.) as needles, m. p. 321—323°, $\lambda_{max.}$ 230, 252, and 302 mμ (log ε 4·50, 4·35, and 3·90, respectively), $\lambda_{max.}$ (mull) 6·02 μ, 6·13, 6·20, and 6·40 μ [Found: C, 59·8; H, 4·5; O, 29·25; N, 6·2%; OMe, 0·0; equiv. (KOH), 229. $C_{11}H_9O_4N$ requires C, 60·25; H, 4·15; O, 29·2; N, 6·4%; equiv., 219]. This dissolved in dilute aqueous sodium hydroxide and was precipitated on acidification. Treatment in ether with diazomethane at 5° for 24 hr. regenerated casimiroin almost quantitatively.

N-Benzoyltyramine.—This substance was obtained from the " acid " benzene extract and was eluted from the column with ether–ethyl acetate (4 : 1). It crystallised from ether as plates, m. p. 161—162°, $\lambda_{max.}$ 226 and 273 mμ (log ε 4·27 and 3·37, respectively), $\lambda_{max.}$ (mull) 6·08, 6·21 (w), and 6·32 μ (w) (Found: C, 74·85; H, 6·15; N, 5·95%; *M*, 246. Calc. for $C_{15}H_{15}O_2N$: C, 74·65; H, 6·25; N, 5·8%; *M*, 241) (lit.,[4] m. p. 162°). The *acetate* (acetic anhydride–pyridine; 1 hr.; 90°) formed needles (from acetone–hexane), m. p. 121—122°, $\lambda_{max.}$ 222 mμ (log ε 4·15), $\lambda_{max.}$ (in $CHCl_3$) 5·76, 6·09, 6·26 (w), and 6·36 μ (w) (Found: C, 71·85; H, 6·4; N, 4·85; Ac, 15·5. $C_{17}H_{17}O_3N$ requires C, 72·05; H, 6·05; N, 4·95; Ac, 15·2%). The dibenzoyl derivative was prepared by means of benzoyl chloride and pyridine (1 hr., 90°): chromatography on alumina and crystallisation from acetone gave the derivative, m. p. and mixed m. p. 172—173° (identical infrared spectra).

Fusion of the monobenzoyl derivative with potassium hydroxide and a little water at 280° produced benzoic acid (m. p. and mixed m. p.). Methylation of it with diazomethane produced the methyl ether as plates, m. p. 123—124°, which on oxidation with alkaline potassium permanganate in water yielded *p*-methoxybenzoic acid (m. p. and mixed m. p.).

9-Hydroxy-4-methoxyfurano[3,2-g]benzopyran-7-one (II; R = OH).—This furanocoumarin was isolated from the "acid" methylene chloride extract and crystallised from methanol as yellow needles, m. p. 223—224°, $\lambda_{max.}$ 222, 272, and 314 mμ (log ε 4·47, 4·34, and 4·07, respectively), $\lambda_{max.}$ (mull) 5·80, 6·02 (w), 6·12 (w), and 6·20 μ (Found: C, 62·15; H, 3·4; OMe, 13·25%; *M*, 239. Calc. for $C_{12}H_8O_5$: C, 62·05; H, 3·45; 1OMe, 13·35%; *M*, 232) [reported by Power and Callan[3] for the "yellow phenolic substance," m. p. 215—218°; found: C, 63·6; H, 3·9; reported[9] for (II; R = OH), m. p. 221°]. The furanocoumarin dissolved in aqueous sodium hydroxide to a yellow solution. With concentrated sulphuric acid a red colour and with ferric chloride a yellow colour were produced. The acetate, prepared by use of pyridine and acetic anhydride (1 hr.; 90°), separated from methanol as plates, m. p. 181—182°, $\lambda_{max.}$ 221, 246, 266, and 308 mμ (log ε 4·38, 4·22, 4·24, and 4·13, respectively) (Found: C, 61·7; H, 3·8. Calc. for $C_{14}H_{10}O_6$: C, 61·3; H, 3·65%) (lit.,[9] m. p. 180°). The *benzoate*, obtained by means of benzoyl chloride and pyridine (10 min., 90°), formed prisms, m. p. 203—205°, from chloroform–ether (Found: C, 68·15; H, 3·35. $C_{19}H_{12}O_6$ requires C, 67·85; H, 3·6%).

*iso*Pimpinellin (II; R = OMe).—A solution of the furanocoumarin (II; R = OH) (200 mg.) in methanol (10 c.c.) was treated with ethereal diazomethane at room temperature. Crystallisation from acetone–ether gave *iso*pimpinellin (185 mg.) as light yellow needles, m. p. 150—151°, $\lambda_{max.}$ 222, 240, 248, 268, and 311 mμ (log ε 4·40, 4·13, 4·20, 4·32, and 4·14, respectively), $\lambda_{max.}$ (KBr disc) 5·80 and 6·21 μ (Found: C, 63·75; H, 4·2. Calc. for $C_{13}H_{10}O_5$: C, 63·4; H, 4·1%). An authentic specimen of *iso*pimpinellin (m. p. 150—151°) showed identical ultraviolet and infrared spectra and no depression in m. p. was observed on admixture.

Bergaptenquinone (IV).—Chromium trioxide (2·4 g.) in water (10 c.c.) was added to a solution of the furanocoumarin (II; R = OH) (3 g.) in glacial acetic acid (300 c.c.). After 30 min. at room temperature, orange crystals had appeared. The mixture was diluted with water, and the precipitate was collected, washed with water, dried, and crystallised from acetone. The resulting bergaptenquinone (2·14 g.) formed orange plates, m. p. 251—253° (decomp.), $\lambda_{max.}$ 273, 314, and 426 mμ (log ε 4·09, 3·80, and 3·28, respectively), $\lambda_{max.}$ (mull) 5·78, 6·02, 6·21 (w), and 6·40 μ (w) (Found: C, 61·5; H, 2·05; OMe, 0·0; *M*, 195. Calc. for $C_{11}H_4O_5$: C, 61·1; H, 1·85%; *M*, 216] (lit.,[7] m. p. 248—250°).

Furan-2:3-dicarboxylic Acid (III).—Potassium permanganate (10 g.) in water (100 c.c.) was added to a stirred solution of the furanocoumarin (II; R = OH) (3 g.) in 5% aqueous sodium hydroxide (100 c.c.) during 30 min. at room temperature. After a further 10 min., the precipitate was removed, then washed with water, and the filtrate after acidification extracted with ethyl acetate. Evaporation and crystallisation from acetone–ether gave furan-2:3-dicarboxylic acid (0·29 g.), m. p. 220—221°, λ_{max} 263 mμ (log ε 4·14) (Found: C, 46·5; H, 2·75. Calc. for $C_6H_4O_5$: C, 46·2; H, 2.6%) (lit.,[8] m. p. 221°).

Zapotinin.—(a) *From the seed.* This substance was isolated from the "acid" methylene chloride extract by chromatography on alumina of the mother-liquors obtained after removal of the furanocoumarin (II; R = OH). *Zapotinin* was eluted from the column with benzene and crystallised from methanol as yellow needles, m. p. 224—225°, $\lambda_{max.}$ 230, 264, and 345 mμ (log ε 4·34, 4·27, and 3·57, respectively), $\lambda_{max.}$ (mull) 5·96, 6·08, and 6·22 μ (Found: C, 65·95; H, 4·95; OMe, 28·55. $C_{18}H_{16}O_6$ requires C, 65·85; H, 4·9; 3OMe, 28·35%). Zapotinin gave an orange colour with concentrated sulphuric acid and a dark green colour with alcoholic ferric chloride. The *acetate* crystallised from ether–methanol as colourless needles, m. p. 214—216°, $\lambda_{max.}$ 226 and 320 mμ (log ε 4·42 and 3·87, respectively) (Found: C, 64·55; H, 4·85. $C_{20}H_{18}O_7$ requires C, 64·85; H, 4·9%).

(b) *From zapotin.* A mixture of zapotin (0·5 g.), potassium hydroxide (5 g.), and water (0·5 c.c.) was heated rapidly to 270° and kept at this temperature for 20 min. The mass was allowed to cool, then dissolved in water, and the solution was acidified with hydrochloric acid. The resulting precipitate on crystallisation from methanol gave zapotinin (0·41 g.), m. p. 223—225°. Identity with the substance isolated from the plant was established by mixed m. p. determination and infrared comparison.

(c) *From demethylzapotin.* Demethylzapotin (50 mg.) in methanol (3 c.c.) was methylated with ethereal diazomethane overnight at room temperature. Crystallisation from methanol gave zapotinin (12 mg.), m. p. 220—222°, undepressed on admixture with the naturally occurring material.

Zapoterin.—This compound was eluted from the column with benzene–methylene chloride (1 : 1) directly after zapotinin. *Zapoterin* formed prisms (from methanol), m. p. 257—259°, $[\alpha]_D$ −51°, no high-intensity ultraviolet absorption maximum, $\lambda_{max.}$ (KBr disc) 5·72, 5·85, 6·01, 6·16, and 6·36 μ (w) (Found : C, 65·75; H, 6·9; O, 27·0%; OMe, 0·0; *M*, 327. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·95; O, 27·55%; *M*, 348). The Molisch test for sugars was negative. Zapoterin gave a brown colour with concentrated sulphuric acid and a deep yellow colour with concentrated nitric acid. Zapoterin with acetic anhydride and pyridine at 90° for 1 hr. gave iso*zapoterin*, needles (from methanol), m. p. 284—285°, $\lambda_{max.}$ (KBr disc) 5·78, 5·86, and 6·12 μ (w) (Found : C, 65·4; H, 6·9; Ac, 0·0. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·95%.)

Casimirolid.—The chromatogram from which zapotinin and zapoterin had been removed was washed with methylene chloride. This resulted in the elution of casimirolid, prisms (from ethanol), m. p. 229—231°, $[\alpha]_D$ −49°, no high-intensity ultraviolet absorption maximum, $\lambda_{max.}$ (in $CHCl_3$), 5·78, 5·92, 6·12 (w), and 6·28 μ (w) (Found : C, 67·8; H, 6·5; O, 25·9%; *M*, 487. Calc. for $C_{28}H_{32}O_6$: C, 67·7; H, 6·5; O, 25·8%; *M*, 496). (Power and Callan [2] give m. p. 229—230°, $[\alpha]_D$ −49°; found : C, 69·5; H, 6·9%; *M*, 426.)

β-*Sitosterol* β-D-*Glucoside.*—This substance was obtained from the " acid " pentyl alcohol extract. It crystallised directly from dioxan and had m. p. 290—295° (decomp.) (Found : C, 72·75; H, 10·25. Calc. for $C_{35}H_{60}O_6$: C, 72·85; H, 10·5%) (lit.,[14] m. p. 285—290°). The tetra-acetate had m. p. 164—166° (lit.,[14] m. p. 166—168°).

Eduline.—The " alkaline " benzene extract on chromatography, elution with benzene–ether (9 : 1), and crystallisation from acetone–ether gave *eduline* as plates, m. p. 187—188°, $\lambda_{max.}$ 256, 336, and 350 mμ (log ε 4·53, 4·04, and 4·06, respectively), $\lambda_{max.}$ (in $CHCl_3$) 6·18 (w), 6·27, and 6·40 μ (Found : C, 76·95; H, 5·8; N, 5·2; OMe, 11·5. $C_{17}H_{15}O_2N$ requires C, 76·95; H, 5·7; N, 5·3; 1OMe, 11·7%). Eduline gave a red colour with tetranitromethane and a violet colour with concentrated nitric acid. The *picrate* separated from methanol as golden-yellow needles, m. p. 225—227° (decomp.) (Found : C, 56·2; H, 3·7; N, 11·5. $C_{17}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 55·85; H, 3·65; N, 11·35%). The *perchlorate*, prepared in acetone, crystallised from acetone–ether as needles, m. p. 250—252° (Found : C, 55·65; H, 4·45; N, 3·9. $C_{17}H_{15}O_2N,HClO_4$ requires C, 55·8; H, 4·4; N, 3·85%).

Zapotidine.—The " alkaline " methylene chloride extract on chromatography, elution with benzene, and crystallisation from ether furnished *zapotidine* as plates, m. p. 96—98°, $\lambda_{max.}$ 236, 256, and 290 mμ (log ε 3·89, 3·91, and 3·87, respectively), $\lambda_{max.}$ (mull) 6·04 (w), 6·13, and 6·27 μ (Found : C, 50·5; H, 5·4; N, 25·15; S, 19·4; *N*-CH_3, 6·85%; *M*, 170; equiv., 167. $C_7H_9N_3S$ requires C, 50·3; H, 5·45; N, 25·15; S, 19·15; 1*N*-Me, 9·0%; *M*, 167). The *picrate* separated from methanol as yellow laths, m. p. 195—196° (Found : C, 39·35; H, 3·1; N, 21·2. $C_7H_9N_3S,C_6H_3O_7N_3$ requires C, 39·4; H, 3·05; N, 21·2%).

Casimiroedine.—Casimiroedine was obtained from the " alkaline " pentyl alcohol extract by direct crystallisation from pentyl alcohol or methanol as needles, m. p. 224—225°, $[\alpha]_D$ −33° (aq. 1% HCl), $\lambda_{max.}$ 218 and 280 mμ (log ε 4·12 and 4·24 respectively) (Found : C, 60·6; H, 7·05; N, 8·25. Calc. for $C_{17}H_{24}O_5N_2$: C, 60·7; H, 7·2; N, 8·35%) {lit.,[2] m. p. 222—223°, $[\alpha]_D$ −36·5° (aq. 1% HCl)}.

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805. *The Constituents of* Casimiroa edulis *Llave* et *Lex. Part II.* The Bark.*

By J. Iriarte, F. A. Kincl, G. Rosenkranz, and Franz Sondheimer.

Investigation of the trunk and root bark of the Mexican tree *Casimiroa edulis* Llave *et* Lex. has yielded twelve substances. Of these, three (edulein, edulitine, and edulinine) appear to be new. The remainder are shown to be coumarins (bergapten, *iso*pimpinellin, and scopoletin), furanoquinoline alkaloids (dictamnine, γ-fagarine, and skimmianine), a flavonoid (5 : 6-dimethoxyflavone), and two substances (zapotin and casimiroin) previously isolated from the seed.

In Part I,* the isolation of thirteen substances from the seed of the tree *Casimiroa edulis* Llave *et* Lex. was described. We here report a similar investigation of the bark. Besides casimiroin and zapotin, already obtained from the seed, the trunk bark yielded eight substances (see Table), of which three (edulein, edulitine, and edulinine) appear to be new. It is of interest that casimiroedin, the major constituent of the seed, was absent from the bark.

Compounds obtained from trunk and root bark of Casimiroa edulis.

Compound	Extraction solvent	Yield (%) from trunk bark	Yield (%) from root bark
Zapotin	" Acid " benzene	0·122	0·425
Bergapten	,, ,,	—	0·0035
*iso*Pimpinellin	,, ,,	—	0·0122
5 : 6-Dimethoxyflavone	,, benzene and methylene chloride	0·0122	0·645
Casimiroin	,, ,, ,,	0·0052	0·225
Edulein	,, methylene chloride	0·0021	0·0430
Edulitine	,, ,, ,,	0·0006	—
Scopoletin	,, ,,	0·0015	—
Dictamnine	" Alkaline " benzene	0·0008	0·0038
γ-Fagarine	,, ,,	0·0024	0·0106
Skimmianine	,, ,,	0·0020	—
Edulinine	,, methylene chloride	0·0030	0·0026

The extraction procedure was that used previously. The " acid " benzene extract of the trunk bark on chromatography on alumina yielded zapotin and casimiroin, and a compound, $C_{15}H_8O_2(OMe)_2$, shown to be 5 : 6-dimethoxyflavone by successive demethylation and acetylation to 5 : 6-diacetoxyflavone. This flavone has not previously been observed in Nature, but has been obtained by a synthesis [1] which was carried out since it was erroneously believed that the naturally occurring primetin possessed the 5 : 6-dihydroxyflavone structure.

The " acid " methylene chloride extract furnished successively edulein, edulitine, and the known coumarin scopoletin. Edulein, $C_{17}H_{15}O_2N$, contained one methoxyl and one *N*-methyl group, but no active hydrogen; its neutral character pointed to the presence of an amide group and the infrared spectrum was compatible with this.

Edulitine (m. p. 235—236°), $C_{11}H_{11}O_3N$, contained two methoxyl but no *N*-methyl groups, and the presence of a hydroxyl group was shown by the active-hydrogen determination and formation of a monoacetate. It therefore appears to be a hydroxydimethoxyquinoline or -*iso*quinoline. It was suspected that it might be 4-hydroxy-6 : 7-dimethoxyquinoline [2] (m. p. 236—237°), but was found to differ from this. Nevertheless, the general resemblance of the infrared and ultraviolet spectra confirms the quinoline structure. Further work on edulein and edulitine is in progress.

Scopoletin (7-hydroxy-6-methoxycoumarin) was identified by the close agreement

* Part I, preceding paper.

[1] Baker, *J.*, 1939, 956.

[2] Riegel, Lappin, Adelson, Jackson, Albisetti, Dodson, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 1264.

between its physical properties as well as those of the 7-acetate and 7-methyl ether with those reported.[3,4,5,6]

The " alkaline " benzene extract on chromatography gave dictamnine,[7] γ-fagarine,[8] and skimmianine,[9] identified by comparison with authentic samples.

The " alkaline " methylene chloride extract furnished an apparently new alkaloid, edulinine, $C_{16}H_{21}O_4N$, containing one methoxyl but no *N*-methyl group.

The root bark was found similarly to contain all these substances (mostly in larger amounts; cf. Table), except edulitine, scopoletin, and skimmianine. In addition, the two furanocoumarins bergapten [10] and *iso*pimpinellin [11] were isolated. Bergapten was identified by conversion into bergaptenquinone, identical with that described in Part I. The structure of *iso*pimpinellin was confirmed by direct comparison.

Experimental

For general experimental details see Part I.

Extraction Procedure.—(a) *Trunk bark.* The bark was collected in the Federal District of Mexico during the month of April. The sun-dried and ground material (50 kg.) was extracted by the procedure outlined for the fruit, the " acid " hexane extraction being omitted.

(b) *Root bark.* The root bark, obtained from the same source, was dried in the sun and ground and 16·5 kg. were processed in the same way as the trunk bark.

5 : 6-Dimethoxyflavone.—This (from both trunk and root bark) was isolated from the " acid " benzene and methylene chloride extracts and was eluted from the column with benzene–ether (9 : 1). It formed plates (from acetone–methanol), m. p. 198—199°, $\lambda_{max.}$ 270, 300, and 325—327 mμ (log ε 4·45, 4·14, and 3·83, respectively), $\lambda_{max.}$ (mull) 6·03, 6·18, and 6·29 μ (Found : C, 72·5; H, 5·1; OMe, 22·1%; *M*, 262. Calc. for $C_{17}H_{14}O_4$: C, 72·35; H, 5·0; 2OMe, 22·0%; *M*, 282) (lit.,[1] m. p. 196°).

With refluxing hydrobromic acid in acetic acid it gave 5 : 6-dihydroxyflavone, m. p. 185—187°, $\lambda_{max.}$ 282 and 362 mμ (log ε 4·44 and 3·42, respectively) (Found : C, 70·6; H, 4·1. Calc. for $C_{15}H_{10}O_4$: C, 70·85; H, 3·95%) (lit.,[1] m. p. 189—190°), converted by acetic anhydride and pyridine into 5 : 6-diacetoxyflavone, needles (from methanol), m. p. 161—162° (Found : C, 67·45; H, 4·3. Calc. for $C_{19}H_{14}O_6$: C, 67·45; H, 4·15%). The m. p. was undepressed on admixture with an authentic sample (m. p. 162—163°) and the infrared spectra were identical.

Edulein.—This *substance* (both trunk and root bark) was obtained from the " acid " methylene chloride extract and was eluted from the column with benzene–ether (4 : 1). It formed needles (from ethyl acetate–methanol), m. p. 200—201°, $\lambda_{max.}$ 250 and 316 mμ (log ε 4·59 and 4·19, respectively), $\lambda_{max.}$ (in $CHCl_3$) 6·09, 6·15, 6·20, 6·26, and 6·35 μ (Found : C, 76·95; H, 5·7; N, 5·3; OMe, 11·6; *N*-Me, 5·5%; *M*, 255. $C_{17}H_{15}O_3N$ requires C, 76·95; H, 5·7; N, 5·3; 1OMe, 11·65; 1*N*-Me, 5·65%; *M*, 265). Edulein gave a yellow colour with tetranitromethane and an orange colour with alcoholic ferric chloride. *Edulein picrate* formed yellow needles (from methanol), m. p. 191—192° (Found : C, 55·6; H, 3·6. $C_{17}H_{15}O_3N,C_6H_3O_7N_3$ requires C, 55·85; H, 3·65%).

Edulitine.—Edulitine (from the trunk bark only) was eluted from the column, directly after edulein, by ether. Crystallization from ethyl acetate gave needles, m. p. 235—236°, $\lambda_{max.}$ 222, 248, 280, and 320 mμ (log ε 4·43, 4·52, 3·88, and 3·57, respectively), $\lambda_{max.}$ (mull) 6·08, 6·16, and 6·28 μ (Found : C, 64·25; H, 5·45; N, 6·85; OMe, 29·7; active H, 0·49%; *M*, 201. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·85; 2OMe, 30·25; active H, 0·49%; *M*, 205). A m. p. depression was observed on admixture with 4-hydroxy-6 : 7-dimethoxyquinoline,[1] m. p. 232—234°, $\lambda_{max.}$ 224, 246, 318, and 330 mμ (log ε 4·25, 4·47, 3·99, and 4·01, respectively), $\lambda_{max.}$ (mull) 6·08, 6·19, and 6·43 μ. Edulitine gave a yellow colour with 20% aqueous potassium hydroxide and a magenta colour with alcoholic ferric chloride. The *picrate* formed small yellow needles (from methanol), m. p. 189—191° (Found : C, 47·05; H, 3·05. $C_{11}H_{11}O_3N,C_6H_3O_7N_3$ requires C,

[3] *Inter al.*, Schmidt, *Arch. Pharm.*, 1898, **236**, 324.
[4] Power and Rogerson, *J.*, 1912, **101**, 5.
[5] Sera and Shibuye, *J. Agric. Chem. Soc. Japan*, 1930, **6**, 600.
[6] Araki and Miyashita, *J. Pharm. Soc. Japan*, 1929, **49**, 736.
[7] *Inter al.*, Asahina, Ohta, and Inubuse, *Ber.*, 1930, **63**, 2045.
[8] *Inter al.*, Deulofeu, Labriola, and de Langhe, *J. Amer. Chem. Soc.*, 1942, **64**, 2326.
[9] *Inter al.*, Asahina and Inubuse, *Ber.*, 1930, **63**, 2052.
[10] *Inter al.*, Thomas and Baetcke, *Ber.*, 1912, **45**, 3705; Howell and Robertson, *J.*, 1937, 293.
[11] *Inter al.*, Wessely and Kallab, *Monatsh.*, 1932, **59**, 161.

47·0; H, 3·25%). The *monoacetate* had m. p. 200—201°, $\lambda_{max.}$ 238, 314, and 326 mμ (log ε 4·36, 3·87, and 3·89, respectively) (Found: C, 62·95; H, 5·3. $C_{13}H_{13}O_4N$ requires C, 63·15; H, 5·3%).

Scopoletin.—The chromatogram (from the trunk bark only) after removal of edulein and edulitine was washed with ethyl acetate–methanol (1 : 1); the resulting yellow solid which did not melt below 330° was dissolved in water. Amberlite ion-exchange resin IR-120 (3 parts) was added, the supernatant liquid decanted, and the resin washed with methanol. The combined solutions were evaporated and the residue was crystallized from methanol–ether. This procedure yielded scopoletin as needles, m. p. 203—204°, $\lambda_{max.}$ 228, 297, and 347 mμ (log ε 4·12, 3·67, and 4·07, respectively), $\lambda_{max.}$ (in $CHCl_3$) 5·80, 6·16 (w), and 6·30 μ (Found: C, 62·75; H, 4·25; OMe, 16·2%; *M*, 202. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2; 1OMe, 16·15%; *M*, 192) (lit.,[4] m. p. 203—204°). Scopoletin acetate formed plates (from acetone), m. p. 177°, $\lambda_{max.}$ 224, 277, and 335 mμ (log ε 4·44, 4·07, and 3·95, respectively) (Found: C, 61·7; H, 4·35. Calc. for $C_{12}H_{10}O_5$: C, 61·55; H, 4·3%) (lit.,[4] m. p. 177°). Scopoletin methyl ether, made by means of diazomethane, separated as needles (from methanol), m. p. 144—145° (Found: C, 64·35; H, 4·95; O, 31·05. Calc. for $C_{11}H_{10}O_4$: C, 64·05; H, 4·9; O, 31·05%) (lit., m. p. 145°[5]; 147—148°[6]).

Dictamnine.—This furanoquinoline (from both trunk and root bark) was isolated from the "alkaline" benzene extract and was eluted with benzene–ether (9 : 1). It formed needles (from acetone–hexane), m. p. 132—133°, $\lambda_{max.}$ 236, 309, and 328 mμ (log ε 4·78, 3·96, and 3·88, respectively), $\lambda_{max.}$ (mull) 6·10, 6·27, and 6·41 μ (w) (Found: C, 72·7; H, 4·4; N, 7·05; OMe, 15·5%; equiv., 196; *M*, 194. Calc. for $C_{12}H_9O_2N$: C, 72·35; H, 4·55; N, 7·05; 1OMe, 15·6%; equiv. = *M*, 199). Identity with a sample (m. p. 131—132°) was established through mixed m. p. and infrared comparison. Dictamnine picrate separated from methanol as light yellow prisms, m. p. 165—166° (Found: C, 50·55; H, 2·9; N, 13·3. Calc. for $C_{12}H_9O_2N,C_6H_3O_7N_3$: C, 50·45; H, 2·85; N, 13·1%) (lit.,[7] m. p. 163°).

γ-Fagarine.—This substance (from trunk and root bark) was eluted after dictamnine with benzene–ether (7 : 3). Crystallization from acetone–ether gave rhombs, m. p. 141—142°, $\lambda_{max.}$ 244, 310, and 336 mμ (log ε 4·79, 3·86, and 3·78, respectively), $\lambda_{max.}$ (mull) 6·10, 6·27, and 6·41 μ (w) (Found: C, 68·1; H, 4·85; N, 6·3; OMe, 27·05%; equiv., 215; *M*, 201. Calc. for $C_{13}H_{11}O_3N$: C, 68·1; H, 4·85; N, 6·1; 2OMe, 27·05%; equiv. = *M*, 229). An authentic sample, m. p. 141—142°, was identical (mixed m. p.; infrared). The picrate, yellow plates from methanol, had m. p. 175—176° (Found: C, 49·95; H, 3·0; N, 12·4. Calc. for $C_{13}H_{11}O_3N,C_6H_3O_7N_3$: C, 49·8; H, 3·1; N, 12·2%) (lit.,[8] m. p. 177°).

Skimmianine.—Skimmianine (from trunk bark only) was eluted with benzene–ether (1 : 1) directly after γ-fagarine. It separated from methanol as wedges, m. p. 178°, $\lambda_{max.}$ 248, 320, and 331 mμ (log ε 4·88, 3·91, and 3·91, respectively), $\lambda_{max.}$ (mull) 6·10, 6·25, and 6·40 μ (w) (Found: C, 64·7; H, 4·9; N, 5·65; OMe, 32·45; equiv., 223; *M*, 236. Calc. for $C_{14}H_{13}O_4N$: C, 64·85; H, 5·05; N, 5·4; 3OMe, 35·9%; equiv. = *M*, 259). Identity with an authentic specimen, m. p. 178—179°, was established in the usual way. The picrate formed yellow needles (from methanol), m. p. 195—196° (Found: C, 49·2; H, 3·55; N, 11·6. Calc. for $C_{14}H_{13}O_4N,C_6H_3O_7N_3$: C, 49·2; H, 3·3; N, 11·5%) (lit.,[9] m. p. 195—197°).

Edulinine.—This *alkaloid* (from both trunk and root bark) was obtained by chromatography of the "alkaline" methylene chloride extract on silica. The fractions eluted with ethyl acetate separated from this solvent as plates, m. p. 140—142°, $\lambda_{max.}$ 228, 274, 282, and 324 mμ (log ε 4·61, 3·93, 3·90, and 3·91, respectively), $\lambda_{max.}$ (mull) 6·10 and 6·25 μ (Found: C, 65·85; H, 7·2; N, 4·8; OMe, 10·8; *M*, 262. $C_{16}H_{21}O_4N$ requires C, 65·95; H, 7·25; N, 4·8; 1OMe, 10·65%; *M*, 291). The methylenedioxy-group was absent, as indicated by the gallic acid colour test. Likewise the vanillin test for indoles was negative. Edulinine gave an intense yellow colour with tetranitromethane.

Bergapten.—This substance (from root bark only) was isolated from the "acid" benzene extract by repeated chromatography on alumina. The first fractions eluted with benzene–ether (9 : 1) on crystallization from methanol gave bergapten as needles, m. p. 187—188°, $\lambda_{max.}$ 250, 260, 268, and 310 mμ (log ε 4·24, 4·21, 4·24, and 4·16, respectively), $\lambda_{max.}$ (mull) 5·78, 6·13, 6·21, and 6·30 μ (Found: C, 66·7; H, 4·0; O, 29·3; OMe, 14·7%; *M*, 212. Calc. for $C_{12}H_8O_4$: C, 66·65; H, 3·75; O, 29·6; 1OMe, 14·35%; *M*, 216) (lit.,[10] m. p. 188—189°).

Successive nitration, reduction, and oxidation of bergapten, carried out as described previously,[10] yielded bergaptenquinone, m. p. and mixed m. p. 250—253°.

iso*Pimpinellin.*—This compound (from root bark only) was eluted with benzene–ether (9 : 1) after bergapten. It formed pale yellow needles (from methanol), m. p. 149—150° (Found: C,

63·6; H, 4·25. Calc. for $C_{13}H_{10}O_5$: C, 63·4; H, 4·1%). The m. p. was undepressed on admixture with the sample (m. p. 150—151°) described in the previous paper and the infrared and ultraviolet spectra were identical.

The authors thank Mr. Santiago Fuentes of the Botanical Department, Syntex S.A., for collection of the plant material, Professor W. Baker for the sample of 5 : 6-diacetoxyflavone, Professor Tatsuo Ohta of the Tokyo College of Pharmacy for the sample of dictamnine, Professor V. Deulofeu of Buenos Aires for samples of γ-fagarine and skimmianine, and Dr. B. Riegel of G. D. Searle and Co., Chicago, for the sample of 4-hydroxy-6 : 7-dimethoxy quinoline.

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806. *Syntheses in the Quinazolone Series. Part II.* Synthesis of Quino- and Quinazo-quinazolones.*

By (MRS.) T. STEPHEN and HENRY STEPHEN.

The synthesis of quinazolones has now been extended to the condensation of methyl anthranilate and of ammonium anthranilate with cyclic imidoyl chlorides, *i.e.*, compounds containing –N:CCl– as part of a ring structure, *viz.*, 2-chlorolepidine and its derivatives and 4-chloro- and 4-chloro-2-phenyl-quinazoline.

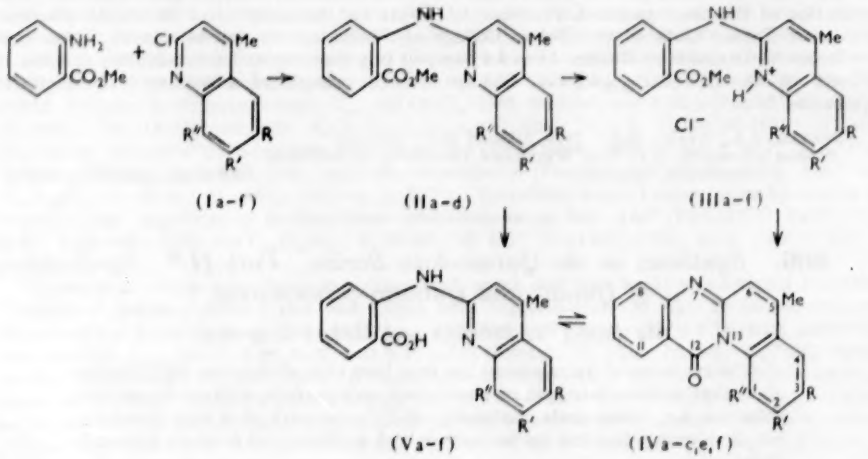
METHYL ANTHRANILATE condenses with 2-chlorolepidine (Ia) in two stages, giving at 140° an 80% yield of methyl *N*-2′-lepidylanthranilate but at 170—200° a quantitative yield of 5-methylquino[2,1-*b*]quinazol-12-one (IV) (Ring Index No. 2658). The latter product arises by conversion of the ester (II), by the hydrogen chloride liberated during the condensation, into the hydrochloride (III), the cation of which cyclises. Similarly, at 140° 2-chloro-4 : 6- (Ib), -4 : 7- (Ic) and -4 : 8-dimethylquinoline (Id) condense with methyl anthranilate, yielding respectively the esters (IIb—d). The chlorine atoms in 2-chloro-6-methoxy- (Ie) and -ethoxy-lepidine (If) are less reactive, since these compounds do not condense with methyl anthranilate at 140°: however, at 170° condensation takes place, and the products are mixtures of the esters and the quinoquinazolones; at 200° only the latter are obtained (95% yield). Likewise, 2-chlorolepidine and its 6- and 7-methyl derivatives (Ia and b) with methyl anthranilate at 200° give excellent yields of the corresponding quinazolones, (IVa—c). The product (IVa) is identical with that described by Bose and Sen [1] and Seide and Tschelencev.[2] Condensation of 2-chloro-4 : 8-dimethylquinoline (Id) with methyl anthranilate at its b. p. gives only *N*-(4 : 8-dimethyl-2-quinolyl)-anthranilic acid (Vd), produced by the action of hydrogen chloride on the ester (IId). Failure to effect cyclisation of the acid (Vd) or its ester (IId) is probably due to steric hindrance by the 8-methyl group. All the esters (II) are readily hydrolysed by alcoholic sodium hydroxide to the corresponding acids. Further, *N*-(6-methoxy-2-lepidyl)- (Ve) and *N*-(6-ethoxy-2-lepidyl)-anthranilic acid (Vf) were obtained by alkaline hydrolysis of the quinoquinazolones (IVe and f). All the acids except (Vd), when heated above the m. p. or boiled with acetic anhydride, are converted into the quinoquinazolones.

Attempts to condense 2-chlorolepidine and derivatives with ammonium anthranilate were unsuccessful. At room temperature there is no reaction and at higher temperatures ammonium anthranilate dissociates into ammonia and anthranilic acid, which then condenses with 2-chlorolepidine to give 5-methylquino[2,1-*b*]quinazol-12-one (IVa). This had previously been obtained by the same reaction by Ephraim [3] who designated it

* Part I, Levy and Stephen, *J.*, 1956, 985.

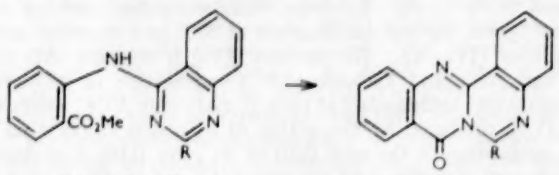
[1] Bose and Sen, *J.*, 1931, 2840.
[2] Seide and Tschelencev, *J. Gen. Chem. Russ.*, 1937, **7**, 2314.
[3] Ephraim, *Ber.*, 1892, **25**, 2710.

N-2-lepidylanthranil, and Backeberg [4] repeating Ephraim's experiment obtained the same compound and accepted the anthranil structure. Bose and Sen [1] had already shown that the compound is a quinazolone, and this structure was later confirmed by Bose [5] and by Seide and Tschelencev.[2]



a, R = R′ = R″ = H. d, R″ = Me, R = R′ = H.
b, R = Me, R′ = R″ = H. e, R′ = OMe, R = R″ = H.
c, R′ = Me, R = R″ = H. f, R′ = OEt, R = R″ = H.

Condensation of methyl anthranilate with 4-chloro- and 4-chloro-2-phenyl-quinazoline gave respectively methyl *N*-4′-quinazolinyl- (VIa) and methyl *N*-(2-phenyl-4-quinazolinyl)-anthranilate (VIb). Under the influence of hydrogen chloride both esters cyclise to quinazo[4,3-*b*]quinazol-8-ones (VIIa and b). The acids corresponding to (VI) are readily



(VI) a: R = H
b: R = Ph

(VII) a: R = H
b: R = Ph

obtained by condensing 4-chloro- and 4-chloro-2-phenyl-quinazoline with ammonium anthranilate in acetone at 0°. Both acids cyclise in refluxing acetic anhydride to the quinazolones (VII). Aggarawal and Ray [6] claim to have obtained the compound (VIIb) by condensing 2-phenylquinazol-4-one with anthranilic acid in phosphorus trichloride and give the m. p. 241—242°, whereas the m. p. of our product is 292°. Their product has been shown to have been a mixture of 2-phenylquinazol-4-one and *N*-(2-phenyl-4-quinazolinyl)anthranilic acid.

[4] Backeberg, *J.*, 1933, 390.
[5] Bose, *Current Sci.*, 1934, **2**, 430.
[6] Aggarawal and Ray, *J. Indian Chem. Soc.*, 1929, **6**, 735.

Experimental

In the condensation of 2-chlorolepidine and its derivatives with methyl anthranilate, it was found that if equimolecular proportions of the reactants were used the yield of condensation product was 10—30% lower than if one mol. excess of methyl anthranilate was used. The condensation in all cases was carried out as follows :

2-Chlorolepidine or its derivative (1 mol.) was heated with methyl anthranilate (2 mol.) in an oil-bath and the temperature of condensation recorded. When separation of methyl anthranilate hydrochloride was considered complete, the mixture was made alkaline with ammonia, and steam-distilled in order to remove excess of methyl anthranilate and any unchanged lepidine (which distils in steam slowly without decomposition after all the methyl anthranilate has been removed).

Methyl N-2′-Lepidylanthranilate (IIa).—2-Chlorolepidine (1·7 g.) and methyl anthranilate (2·7 g.) were heated at 130° for 10 min. The product, m. p. 133—138° (1·5 g.), readily crystallised from ethanol in cream-coloured needles, m. p. 149° (Found : C, 74·35; H, 5·6; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%).

5-Methylquino[2,1-b]quinazol-12-one (IVa).—2-Chlorolepidine (1·7 g.) and methyl anthranilate (2·7 g.), heated together at 170° for 15 min., gave 100% yield of the quinazolone (IVa), which crystallises from ethanol in yellow needles, m. p. 213°, in agreement with Bose and Sen.[1] The product readily forms a hydrochloride, soluble in ethanol. Addition of platinic chloride to this solution gives a buff *platinichloride* [Found : Pt, 20·6. $(C_{17}H_{12}ON_2)_2,H_2PtCl_6$ requires Pt, 20·9%]. The ester (IIa) is readily soluble in concentrated hydrochloric acid but from boiling acid the hydrochloride of (IVa) separates. This on treatment with water and neutralisation liberates the base (IVa), m. p. 213°.

N-2′-Lepidylanthranilic Acid (Va).—An alcoholic solution of the ester (IIa) was refluxed with 10% sodium hydroxide solution for ½ hr., cooled, and acidified with acetic acid. The precipitated acid (Va) crystallised from ethanol in yellow needles, m. p. 203—204° (Found : C, 73·4; H, 4·9; N, 9·9. Calc. for $C_{17}H_{14}O_2N_2$: C, 73·4; H, 5·0; N, 10·1%).

Methyl N-(4 : 6-Dimethyl-2-quinolyl)anthranilate (IIb).—2-Chloro-4 : 6-dimethylquinoline (1 g.) and methyl anthranilate (1·6 g.) at 140° (½ hr.) gave a 50% yield of the ester (IIb), and 2-chloro-4 : 6-dimethylquinoline (0·4 g.) was recovered during steam-distillation. The *product* (IIb) crystallises from 75% dioxan in almost white needles, m. p. 162·5° (Found : C, 74·5; H, 6·0; N, 9·2. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·9; N, 9·15%). Several attempts were made to improve the yield, but condensation for a longer period at 140° or at 140—150° gave mixtures of (IIb) and the quinazolone (IVb). When the reactants were refluxed for several hours in dry dioxan, they were recovered unchanged.

Methyl N-(4 : 7-Dimethyl-2-quinolyl)anthranilate (IIc).—2-Chloro-4 : 7-dimethylquinoline (1 g.) and methyl anthranilate (1·6 g.) at 140° (½ hr.) gave 80% of the *ester* (IIc) which crystallised from 75% dioxan in almost white needles, m. p. 172° (Found : C, 74·3; H, 6·0. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·9%). Condensation at 170—190° gave an inseparable mixture of the quinazolone (IVc) and the ester (IIc), which was entirely converted into the quinazolone (IVc) by boiling concentrated hydrochloric acid or hydrolysed to the acid (Vc) by sodium hydroxide.

Table 1. *Substituted quino[2,1-b]quinazol-12-ones* (IV).

	Condensation					Found (%)			Required (%)		
Product [a]	Temp.	Time (min.)	Yield (%)	M. p.	Formula	C	H	N	C	H	N
IVb	170°	15	93	199°	$C_{18}H_{14}ON_2$	78·6	5·3	10·0	78·8	5·1	10·2
IVc	200—220	—	100	194·5	,,	78·6	5·4	10·1	78·8	5·1	10·2
IVe	,,	10	96	230	$C_{18}H_{14}O_2N_2$	74·5	4·9	9·8	74·5	4·8	9·65
IVf	,,	10	95	193	$C_{19}H_{16}O_2N_2$	75·0	5·4	9·3	75·0	5·3	9·2

[a] All yellow needles from dioxan, except (IVb) which was crystallised from ethanol. *Platinichlorides*, B_2,H_2PtCl_6, were obtained as orange needles from (IVc) (Found : Pt, 20·0. Reqd. : Pt, 20·3%), (IVe) (Found : Pt, 19·5. Reqd. : Pt, 19·6), and (IVf) (Found : Pt, 19·1%. Reqd. : Pt, 19·5). The base (IVb) gave a buff *salt*, $B_2,H_2PtCl_6,2(B,HCl)$ (Found : Pt, 12·3. Reqd. : Pt, 12·3%).

Methyl N-(4 : 8-Dimethylquinolyl)anthranilate (IId).—Condensation of 2-chloro-4 : 8-dimethylquinoline (1 g.) with methyl anthranilate (1·6 g.) at 140° for 10 min. gave 80% of the

ester (IId), crystallising from ethanol in almost white needles, m. p. 170° (Found : C, 74·4; H, 6·0; N, 9·0. $C_{19}H_{16}O_2N_2$ requires C, 74·5; H, 5·8; N, 9·15%).

Analogous Products.—Table 1 records the *quinoquinazolones* prepared as above.

Table 2 records the *N-quinolylaminoanthranilic acids* (V) prepared from the ester (II) and/or the quinoquinazolone (IV) by hydrolysis with sodium hydroxide in boiling aqueous dioxan for

TABLE 2. *Substituted N-quinolylaminoanthranilic acids* (V).

Product [a]	Starting material	Time of hydrol. (hr.)	M. p.[b]	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Vb	IIb	0·5	236°	$C_{18}H_{16}O_2N_2$	73·6	5·7	9·5	74·0	5·5	9·6
Vc	IIc, IVc	0·5	242	"	73·5	5·6	—	74·0	5·5	—
Ve	IVe	1	218	$C_{18}H_{16}O_3N_2$	70·1	5·15	9·2	70·1	5·2	9·1
Vf	IVf	1	188	$C_{19}H_{18}O_3N_2$	70·7	5·7	8·6	70·8	5·6	8·7

[a] All yellow needles from dioxan, except that (IVc) was crystallised from 75% dioxan. [b] With evolution of CO_2.

the time stated. These acids, except (Vf), were converted into quinoquinazolones when sublimed or boiled with acetic anhydride.

The following notes record additional information about these compounds.

Bose and Sen [1] condensed 2-chloro-4 : 7-dimethylquinoline with anthranilic acid and claim to have obtained (IVc), crystallising from acetone in colourless needles, m. p. 150°. On hydrolysis of this compound they claim to have obtained the acid (Vc), m. p. 226°. The only evidence Bose and Sen [1] put forward in support of the constitution of these compounds is analyses for nitrogen.

No condensation occurred between 2-chloro-6-ethoxylepidine and methyl anthranilate below 150°, or when the components were refluxed in solvents such as toluene or xylene for 2—4 hr. Condensation at 150—170° resulted in mixtures which could either be converted into the quinazolone (IVf) by boiling with hydrochloric acid, or hydrolysed to the acid (Vf) by sodium hydroxide.

3-Methoxy-5-methylquino[2,1-b]*quinazol-12-one* (IVe).—2-Chloro-6-methoxylepidine (2 g.) and methyl anthranilate (2·7 g.) did not condense below 150°. Reaction at 150—160° (½ hr.) gave mixtures of probably the expected ester and the quinazolone (IVe), which could not be separated, but when boiled with concentrated hydrochloric acid gave only quinazolone (IVe). Hydrolysis with alcoholic sodium hydroxide converted the mixture into the acid (Ve). Condensation of 2-chloro-6-methoxylepidine with methyl anthranilate at 200—220° for 10 min. resulted in a 96% yield of the quinoquinazolone (IVe). It crystallised from dioxan in canary-yellow needles, m. p. 230° (Found : C, 74·5; H, 4·9; N, 9·8%).

N-(4 : 8-Dimethyl-2-quinolyl)anthranilic Acid (Vd).—When 2-chloro-4 : 8-dimethylquinoline (1 g.) and excess of methyl anthranilate were heated to the b. p. (approx. 250°) until all signs of reaction had ceased, the product was the acid (Vd). In this condensation, the ester (IId) first formed failed to undergo ring closure but the hydrogen chloride present hydrolysed the ester group. The *acid* crystallised from dioxan in yellow needles, m. p. 240° (Found : C, 73·6; H, 5·55; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). All attempts to bring about ring closure by heating it above the m. p. or boiling it with acetic anhydride failed. The ester (IId) in dioxan on hydrolysis with 10% sodium hydroxide yielded the acid (Vd), m. p. 240°. On boiling the acid (Vd) with concentrated hydrochloric acid, pale cream-coloured crystals separated. These contained ionisable chlorine and analysed as the *hydrochloride* of the acid (Vd) (Found : *M*, by titration, 331·5. $C_{18}H_{16}O_2N_2$,HCl requires *M*, 328·5).

Methyl N-4'-Quinazolinylanthranilate (VIa).—To 4-chloroquinazoline (3 g., 1 mol.) in dry acetone methyl anthranilate (2 mols., 5·6 g.) was added. After a few min. the temperature rose from 18° to 28° and a copious white precipitate separated. After 1 hr. this was filtered off and dried (5·6 g., m. p. 195° with effervescence). The acetone filtrate and washings on evaporation yielded unchanged methyl anthranilate (2·5 g.). The precipitate contained ionisable chlorine, was completely soluble in cold water, and addition of aqueous ammonia precipitated the *base* (VIa) which crystallised from dioxan in white needles, m. p. 211° (Found : C, 68·5; H, 4·6; N, 15·3. $C_{15}H_{13}O_2N_3$ requires C, 68·8; H, 4·65; N, 15·05%). The *hydrochloride* had m. p. 195° (Found : *M*, 308·3; N, 13·3%. $C_{15}H_{13}O_2N_3$,HCl requires *M*, 315·5; N, 13·3%).

Quinazo[4,3-b]*quinazol-8-one* (VIIa).—The ester (VIa) was heated at its m. p. until effervescence ceased. The *product* crystallised from ethanol in pale cream-coloured needles, m. p. 197° (Found : C, 72·3; H, 3·85; N, 16·9. $C_{15}H_9ON_3$ requires C, 72·8; H, 3·6; N, 17·0%).

N-4'-Quinazolinylanthranilic Acid.—To a solution of 4-chloroquinazoline (1 mol., 2 g.) in acetone (20 c.c.) at 0°, ammonium anthranilate (1 mol., 2 g.) in acetone (200 c.c.) at 0° was added. There was an immediate precipitate of ammonium chloride. After an hour this was filtered off and the filtrate evaporated under reduced pressure, leaving a yellow solid which did not crystallise from any organic solvents. The *acid* was purified by dissolution in hot sodium carbonate solution and reprecipitation by acetic acid, then being a pale yellow solid, m. p. 248° (decomp.) (Found: C, 67·7; H, 4·3; N, 15·9. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·15; N, 15·8%). The *platinichloride* was obtained by treating a solution in acetone containing concentrated hydrochloric acid with platinic chloride [Found: C, 20·6. $(C_{15}H_{11}O_2N_3)_2.H_2PtCl_6$ requires Pt, 20·7%]. Heating the acid at 250° until effervescence ceased converted it into the quinazolone (VIIa), m. p. 197°.

Methyl N-(*2-Phenyl-4-quinazolinyl*)*anthranilate* (VIb).—4-Chloro-2-phenylquinazoline (1 mol., 2 g.) and methyl anthranilate (2 mols., 2·7 g.) were refluxed in toluene for 2 hr. The mixture was made alkaline with aqueous ammonia and steam-distilled. After the excess of methyl anthranilate had been removed, the residue was slowly volatile in steam, giving cream-coloured needles, m. p. 179°. The bulk of the product crystallised from dioxan to give the same *compound*, m. p. 179° (Found: C, 74·45; H, 4·8; N, 12·0. $C_{22}H_{17}O_2N_3$ requires C, 74·4; H, 4·8; N, 12·2%).

6-Phenylquinazo[4,3-b]*quinazol-8-one* (VIIb).—The ester (VIb), heated under reflux with acetic anhydride for 1 hr., gave, on cooling, pale cream needles, m. p. 292°, of the cyclised *compound* (Found: C, 77·9; H, 4·2; N, 13·1. $C_{21}H_{13}ON_3$ requires C, 78·0; H, 4·0; N, 13·0%).

N-(2-Phenyl-4-quinazolinyl)anthranilic Acid.—The ester (VIb) (0·5 g.) was boiled in dioxan (25 c.c.) and 10% aqueous sodium hydroxide (25 c.c.) under reflux for ½ hr. The *acid* was precipitated with acetic acid, and crystallised from aqueous dioxan in bright yellow needles, m. p. 255° (decomp.) (Found: C, 73·5; H, 4·55; N, 12·6. $C_{21}H_{15}O_2N_3$ requires C, 73·9; H, 4·4; N, 12·7%).

A solution of 2-phenyl-4-chloroquinazoline (1·2 g.) in acetone (50 c.c.) at 0° was added to a solution of ammonium anthranilate (0·8 g.) in acetone (50 c.c.) at 0°. There was an immediate precipitate of ammonium chloride which was filtered off after 1 hr., and the acetone filtrate was evaporated under reduced pressure. The resulting compound was boiled with water to remove anthranilic acid, and then treated with cold aqueous ammonia to separate the acid from 2-phenylquinazol-4-one. Acidification of the ammoniacal solution with acetic acid gave the acid, m. p. 255° (from dioxan). Heating the acid at 255—260° until effervescence ceased gave a mixture, m. p. 220—245°, showing that it does not readily cyclise, probably owing to steric hindrance by the 2-phenyl group. Boiling the acid with acetic anhydride for 1 hr. gave a clear solution, from which after cooling, cream needles, m. p. 292°, identical with the quinazolone (VIIb) were obtained.

4-Chloro-2-phenylquinazoline (0·6 g.) and anthranilic acid (0·7 g.) were boiled under reflux in toluene (20 c.c.) for 1 hr. The toluene was removed under reduced pressure, and the residue boiled with water until free from anthranilic acid. Crystallisation from aqueous dioxan gave a compound, m. p. 240—245° (cf. m. p. 241—242° given for the acid by Aggarawal and Ray [6]). The product was treated with cold aqueous ammonia, and the insoluble portion identified as 2-phenylquinazol-4-one, m. p. 236°. The ammoniacal solution, on acidification with acetic acid, deposited the acid, which after crystallising from dioxan had m. p. and mixed m. p. 255°.

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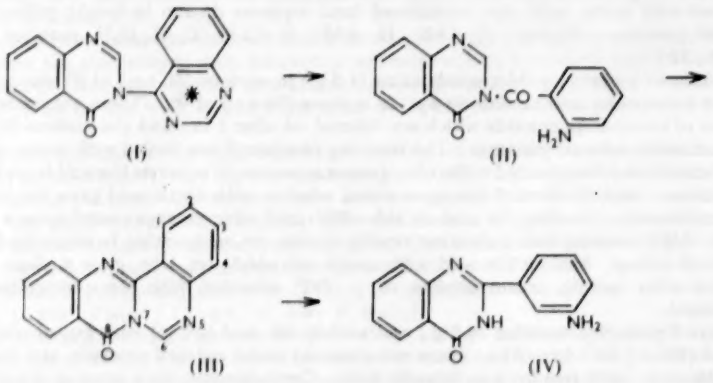
807. *Syntheses in the Quinazolone Series. Part III.* The Formation of Quinazo*[4,3-b]*quinazol-8-one and 2-o-Aminophenylquinazol-4-one by the Hydrolysis of 3-4′-Quinazolinylquinazol-4-one.*

By (Mrs.) T. Stephen and Henry Stephen.

A new method for the preparation of 3-4′-quinazolinylquinazol-8-one (I) and its hydrolysis to quinazo[4,3-*b*]quinazol-8-one (III) and subsequently 2-*o*-aminophenylquinazol-4-one (IV) are described; the conversion of the last compound into 6-substituted derivatives of (III) by acylation is also reported.

3-4′-Quinazolinylquinazol-4-one (I), which is readily obtained by condensation of 4-chloroquinazoline with quinazol-4-one, yields quinazo[4,3-*b*]quinazol-8-one (III) on hydrolysis with 0·1N-hydrochloric acid. Either compound with 2N-hydrochloric acid gives 2-*o*-aminophenylquinazol-4-one (IV), m. p. 241°. A base, m. p. 244°, was obtained by Tomisek and Christensen [1] on hydrolysis of the quinazolone (I) with concentrated hydrochloric acid, but they did not identify it.

Suitable treatment of the product from the action of phosphorus oxychloride on quinazol-4-one yields either the tetracyclic compound (III) or the quinazolone (IV), and formation of the latter can be explained by assuming that quinazol-4-one is partially



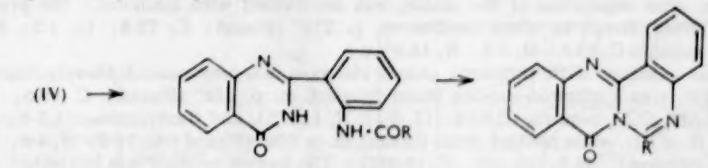
converted into 4-chloroquinazoline which condenses with unchanged quinazolone to give (I). The same explanation will account for the formation of (IV) when 4-chloroquinazoline is partially hydrolysed by water.

Hydrolysis of the compound (I) probably involves the formation of 3-*o*-aminobenzoylquinazol-4-one (II) (not isolated) and elimination of hydrogen cyanide, which is supported by the identification of formic acid and ammonia after hydrolysis of (I). This suggests that the ring marked with an asterisk undergoes fission, subsequent ring closure giving the tetracyclic compound (III). The latter on further hydrolysis yields formic acid and the 2-substituted compound (IV) which on treatment with anhydrous formic acid is reconverted into (III) [which has been independently synthesised [3]]. The product (IV) has been synthesised in this laboratory in another way which will be published later.[2] Condensation of the product (IV) with acetic anhydride gives a mixture of 2-*o*-acetamidophenylquinazol-4-one (V; R = Me) and 6-methylquinazo[4,3-*b*]quinazol-8-one (VI; R = Me), and the former may be converted into the latter by treatment with dilute hydrochloric acid or

* Part II, preceding paper.

[1] Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1948, **70**, 874.
[2] T. A. Kilroe Smith, personal communication.
[3] Stephen and Stephen, preceding paper.

sodium hydroxide solution. Propionic anhydride gives 2-*o*-propionamidophenylquinazol-4-one (V; R = Et) and 6-ethylquinazo[4,3-*b*]quinazol-8-one (VI; R = Et). Benzoic anhydride, fused with (IV), gives 6-phenylquinazo[4,3-*b*]quinazol-8-one (VI; R = Ph), which has previously been synthesised.[3]



Experimental

4-Chloroquinazoline.—Quinazol-4-one (10 g.) in phosphorus oxychloride (60 c.c.) was refluxed with phosphorus pentachloride (15 g.) for 1 hr., excess of phosphorus oxychloride removed under reduced pressure, and the residue distilled at 145°/28 mm. The distillate (12·6 g.) was extracted with light petroleum (b. p. 40—60°; 3 × 150 c.c.), and the combined extracts, evaporated under reduced pressure, yielded 4-chloroquinazoline (9·5 g.), m. p. 96° (Found: equiv., by hydrolysis in aq. NaOH, 165·4. Calc. for $C_8H_5N_2Cl$: equiv., 164·5).

3-4′-Quinazolinylquinazol-4-one (I).—4-Chloroquinazoline (1 g.) was heated with quinazol-4-one (1 g.) at 100° for 15 min.; the reaction was then complete. The product was triturated with cold water, neutralised with aqueous sodium hydrogen carbonate, and filtered off; the residue was treated with boiling water to remove quinazol-4-one and crystallised from ethanol in white needles, m. p. 232° (Found: C, 70·1; H, 3·8; N, 20·3. Calc. for $C_{16}H_{10}ON_4$: C, 70·1; H, 3·6; N, 20·4%).

Conversion of the Compound (I) *into 4-Chloroquinazoline.*—A mixture of the compound (I) (1 g.) and phosphorus pentachloride (1·2 g.) in phosphorus oxychloride (10 c.c.) was refluxed until a pale yellow solution was obtained. Removal of phosphorus oxychloride gave a residue which distilled at 144°/22 mm. The distillate, after solidifying, was extracted with light petroleum (b. p. 40—60°), and yielded 4-chloroquinazoline (0·9 g.), m. p. 96°. It is probable that the amidoyl chloride is formed as an intermediate which dissociates on distillation into two mols. of 4-chloroquinazoline.

Quinazo[4,3-b]*quinazol-8-one* (III).—A solution of the compound (I) (1 g.) in ethanol (10 c.c.), boiled with 0·1N-hydrochloric acid (5 c.c.), deposited the *product* (III) as white needles, m. p. 197° (Found: C, 72·5; H, 3·8; N, 16·9. $C_{16}H_9ON_3$ requires C, 72·8; H, 3·6; N, 17·0%). Formic acid and ammonia were found in the filtrate. Ammonia was also obtained when quinazol-4-one (5 g.) was heated in phosphorus oxychloride (30 c.c.) for 1 hr.; and removal of the excess of chloride under reduced pressure gave a light brown viscous mass which was chilled in ice and neutralised with sodium hydrogen carbonate. The product was filtered off and crystallised from ethanol in needles, m. p. 197° (3·6 g., 86%).

2-*o*-*Aminophenylquinazol-4-one* (IV).—The compound (I) dissolved readily in hot 2N-hydrochloric acid, and the solution on cooling deposited the *aminophenylquinazolone* as white needles which, crystallised from ethanol, had m. p. 241° (Found: C, 70·8; H, 4·8; N, 17·7. $C_{14}H_{11}ON_3$ requires C, 70·8; H, 4·6; N, 17·7%). Formic acid and ammonia were detected. Addition of platinic chloride to a solution of the product in concentrated hydrochloric acid gave a buff *platinichloride* [Found: Pt, 20·3. $(C_{14}H_{11}ON_3)_3,H_2PtCl_6,2HCl$ requires Pt, 20·4%]. The product (IV) was also obtained by refluxing quinazol-4-one (5 g.) in phosphorus oxychloride (30 c.c.) for 1 hr. The residue after removal of excess of oxychloride was boiled with water, and the yellow solution on neutralisation with ammonia gave yellow needles (3·8 g.), m. p. 241°. 4-Chloroquinazoline, moistened with water and heated, reacted vigorously and the resulting product after purification melted at 241°. The base (IV) is slightly soluble in boiling water, and soluble in hot dilute hydrochloric acid from which it crystallised on cooling. It slowly dissolved in boiling sodium carbonate solution, and immediately in cold aqueous ammonia or sodium hydroxide from which it is precipitated on acidification. A solution of the base in anhydrous formic acid, refluxed for ½ hr., cooled, and diluted with water gave the compound (III).

6-Methylquinazo[4,3-*b*]*quinazol-8-one* (VI; R = Me).—The base (IV) (1 g.) was refluxed with acetic anhydride (10 c.c.) for 1 hr., and on addition of water gave a mixture of 2-*o*-*acetamidophenylquinazol-4-one* (V; R = Me) and the base (VI; R = Me), which were separated by

treatment with cold dilute hydrochloric acid in which the latter is soluble. The insoluble portion (V; R = Me) crystallised from aqueous dioxan in needles, m. p. 177° (Found: C, 68·8; H, 4·8; N, 14·8. $C_{16}H_{12}O_2N_2$ requires C, 68·8; H, 4·7; N, 15·0%). The product (V) was converted into the *base* (VI; R = Me) by boiling dilute hydrochloric acid or aqueous sodium hydroxide. The filtrate, after separation of the amide, was neutralised with ammonia; the precipitate crystallised from dioxan in white needles, m. p. 276° (Found: C, 73·6; H, 4·3; N, 15·9. $C_{16}H_{11}ON_2$ requires C, 73·6; H, 4·2; N, 16·0%).

A similar reaction with propionic anhydride gave 2-*o*-*propionamidophenylquinazol*-4-*one* (V; R = Et), cream-coloured needles (from dioxan), m. p. 156° (Found: C, 69·5; H, 4·9; N, 14·4. $C_{17}H_{14}O_2N_2$ requires C, 69·6; H, 5·1; N, 14·3%), and 6-*ethylquinazo*[4,3-b]*quinazol*-8-*one* (VI; R = Et), white needles (from dioxan), m. p. 250° (Found: C, 74·2; H, 4·5; N, 14·8. $C_{17}H_{12}ON_2$ requires C, 74·2; H, 4·7; N, 15·0%). The former product was converted into the latter by boiling dilute hydrochloric acid or aqueous sodium hydroxide.

6-*Phenylquinazo*[4,3-b]*quinazol*-8-*one* (VI; R = Ph).—The base (IV) (0·5 g.) and benzoic anhydride (1 g.) were heated at 250° until reaction ceased (1½ hr.). The product, freed from benzoic acid by treatment with cold sodium carbonate solution, crystallised from dioxan in cream-coloured needles, m. p. and mixed m. p. 292° (Found: C, 77·9; H, 4·2; N, 13·1. Calc. for $C_{21}H_{12}ON_2$: C, 78·0; H, 4·0; N, 13·0%). A buff-coloured *salt* was prepared by addition of platinic chloride to a solution of the base in concentrated hydrochloric acid [Found: Pt, 13·8. $(C_{21}H_{12}ON_2)_2.H_2PtCl_6.C_{21}H_{12}ON_2.HCl$ requires Pt, 13·8%].

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808. *The Polarography of Oximes.*

By H. J. GARDNER and W. P. GEORGANS.

The polarographic behaviour of some alkyl aryl and diaryl ketoximes has been studied in buffered solutions. A wave is given by each compound in the pH range 2—*ca.* 10, and corresponds to the uptake of four electrons. The $E_{\frac{1}{2}}$–pH coefficient is *ca.* −70 mv per pH unit. Reduction of the oxime probably proceeds via the conjugate acid of the oxime, $(R_2C{:}N{\cdot}OH)H^+$, which is expected at the electrode interface as an intermediate. The wave height falls to zero at pH > *ca.* 6, owing probably to the decreasing rate of formation of $(R_2C{:}N{\cdot}OH)H^+$. With some oximes in alkaline solutions there is a second wave which is not clearly differentiated from the solution decomposition current. The maximum wave height is nearly equal to that of the first wave. The $E_{\frac{1}{2}}$–pH coefficient is small. Reduction probably proceeds *via* the initial uptake of four electrons to the neutral oxime.

OXIMES from alkyl aryl and diaryl ketones have been studied polarographically in buffered solutions by Langer,[1] Stone and Furman,[2] and Souchay and Ser.[3] The present work, which was begun before publication by Souchay and Ser,[3] confirms their findings for the the general behaviour of oximes but also suggests phenomena in both acidic and alkaline regions which may be typical of oximes generally.

The oximes studied were derived from benzophenone, phenyl *p*-tolyl ketone, methyl β-naphthyl ketone, acetophenone, methyl *p*-tolyl ketone, and benzoin.

RESULTS

The current–voltage waves of benzophenone oxime in solutions of pH > 2 were typical of the oximes generally (see Fig. 1). The decrease of the first wave height with pH is broadly

[1] Langer, *Ind. Eng. Chem. Anal.*, 1942, **14**, 283.
[2] Stone and Furman, *J. Amer. Chem. Soc.*, 1948, **70**, 3062.
[3] Souchay and Ser, *J. Chim. phys.*, 1952, **49**, 172.

similar to that observed for pyruvic acid [4] but differs by the presence of a maximum and a minimum in the wave between pH 5 and 8. The maxima were not removed by the addition of small amounts of gelatine and the oximes were studied in the absence of a maximum suppressor. Fig. 2 shows plots of the maximum (limiting) currents against pH for the oximes studied.

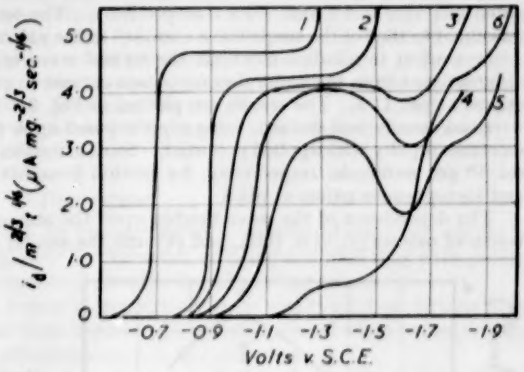

FIG. 1. *Benzophenone oxime*: 1·0mM *with buffer mixture A and* 25% (*vol.*) *ethanol, showing shape of waves at various* pH. *The* pH *values are*: 1, 2·29; 2, 4·56; 3, 5·62; 4, 6·57; 5, 7·65; 6, 9·5.

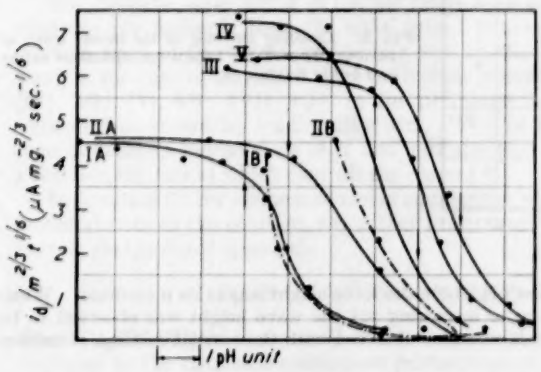

FIG. 2. *Limiting currents of the first wave at various* pH *for* 1·0mM*-solutions of the oximes. The curves are labelled for the particular compound and the buffered solution as described in the text. An arrow shows the position of* pH 7 *for each curve.*

The minimum currents for the first wave were expressed as a percentage of the maximum currents and some examples are given in Table 1, columns 4 and 9. Also recorded in Table 1 are the potentials ($E_{min.}$) at which the minima occur.

TABLE 1.

Compound	Buffer	pH	$i_{min.}/i_{max.}$ (%)	$-E_{min.}$ (v *v.* SCE)	Compound	Buffer	pH	$i_{min.}/i_{max.}$ (%)	$-E_{min.}$ (v *v.* SCE)
$COPh_2$ (I)	A	5·6	92	1·6	β-$C_{10}H_7$·COMe (III)	A	5·8	83	$1·6_5$
		6·5	75	1·6			6·8	55	1·6
		7·5	55	1·6			8·5	54	1·5
		9·0	25	$1·4_5$	Ph·COMe (IV)	A	3·3	97	1·4
,, ...	B	7·5	48	$1·4_5$			6·4	58	$1·6_5$
		8·5	60	$1·3_5$			7·1	43	$1·5_5$
p-C_6H_4Me·COPh (II)	A	9·1	60	$1·4_5$	*p*-C_6H_4Me·COMe (V)	A	5·6	51	$1·6_7$
,,	B	8·1	54	$1·4_5$			6·8	23	$1·6_3$
		9·1	78	$1·3_5$	$(COPh)_2$ (VI) [a]	A	6·23	72	$1·6_5$

[a] See also Langer.[1]

Benzophenone oxime and methyl *p*-tolyl ketoxime were also studied in sulphuric acid–water mixtures. With benzophenone oxime there was a single wave obtained at −0·60 v in 5—20% (w/w) sulphuric acid. The wave height in 5% sulphuric acid was nearly equal to the maximum wave height found in the pH range 2—*ca.* 10. When the solution was kept for 4

[4] Brdička, *Coll. Czech. Chem. Comm.*, 1947, **12**, 212.

days the wave decreased in height by about 50% and moved to more negative potentials. At 50% sulphuric acid two waves of nearly equal height were found at −0·5 and −0·6 v respectively. The total wave height corresponded to that of the single wave above. At higher concentrations of acid the waves were obscured by the solution decomposition current. Methyl *p*-tolyl ketoxime gave two waves of equal height in 10—50% sulphuric acid. The half-wave potentials were −0·7 and −0·8 v respectively. The total wave height in 10% sulphuric acid was equal to that of the single wave obtained in the pH range 2—*ca.* 10.

In neutral to alkaline solutions the second wave of benzophenone oxime was sufficiently differentiated from the buffer decomposition current to permit measurement of the wave height except at pH 11·3. The results are plotted in Fig. 3. The second waves of the other oximes were not usually well-defined, being superimposed upon the buffer decomposition current which increases rapidly with applied potential. Some estimates of $i_d/m^{2/3}t^{1/6}$ are 5·4 and 7·7 μA mg.$^{-2/3}$ sec.$^{-1/6}$ per millimole, respectively, for methyl β-naphthyl ketoxime in the pH range 8—11, and acetophenone oxime at pH 8.

The dependence of the wave heights upon the mercury pressure, H, was tested for the first waves of oximes (I), (II), (III), and (V) and the second wave of oxime (I). The wave heights

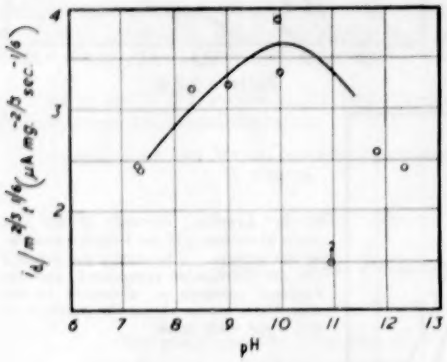

FIG. 3. *Limiting currents of the second wave at various* pH > 7 *for* 1·0mM-*benzophenone oxime and buffer mixture B.*

were found to be linear with $H^{\frac{1}{2}}$ at those pH where the wave height was at its maximum. When the height of the first wave fell owing to increasing pH the wave height was observed to be independent of H. Independence of H was also observed with the current minima of oximes (I) and (II).

The half-wave potentials of the first waves were determined by using the current maxima as the limiting currents. As the pH was increased in the pH range 2—*ca.* 10 the half-wave potentials became more negative. The $E_{\frac{1}{2}}$–pH relations were linear with average deviations from linearity as shown in Table 2. The $E_{\frac{1}{2}}$–pH coefficients are also given in Table 2, together

TABLE 2.

Compound	(I)			(II)		(III)		(IV)		(V)	(VI)
Buffer solution	A	B	B	A	B	A	B	A	B	A	A
Wave (first or second) ...	1st	1st	2nd	1st	1st	1st	2nd	1st	2nd	1st	1st
$E_{\frac{1}{2}}$–pH coefficient (mv per pH unit)	−78	−10	5	−63	0	−71	−10	−71	(0)	−71	−77
pH range	2—8	7—11	9—11	2—10	8—12	2—5	10—11	2—7	11	2—8	4—6
No. of points plotted ...	6	4	4	5	5	3	2	6	1	4	2
Average deviation (mv) from linear $E_{\frac{1}{2}}$–pH relation	2	10	1	13	40	2	—	4	—	5	—
$-E_{\frac{1}{2}}$ at pH 0	0·522	1·07	—	0·525	1·11	0·676	—	0·710	—	0·742	0·68
$-E_{\frac{1}{2}}$ at pH 10	—	—	1·635	—	—	—	1·75	—	1·78	—	—

with the half-wave potential extrapolated to zero pH. For the second wave the $E_{\frac{1}{2}}$–pH coefficients are about zero (see Table 2).

Linear relations between wave height and concentration were obeyed to within 2% at 0·3, 0·6, 1·0, and 1·3mM-concentration by benzophenone oxime, methyl β-naphthyl ketoxime, and methyl *p*-tolyl ketoxime and the straight lines when extrapolated passed through the origin.

The half-wave potentials for both benzophenone oxime and methyl β-naphthyl ketoxime became more negative by 27 mv per 10-fold increase of concentration, and by 13 mv for methyl *p*-tolyl ketoxime. The relation was nearly linear for methyl β-naphthyl ketoxime.

A 20 ml. polarographic solution of benzophenone oxime at pH 5 was reduced *in situ* with 1 mg. of palladium–carbon catalyst and hydrogen. The limiting current decreased to zero but no anodic wave appeared before +0·1 v, even when the solution was made alkaline to pH 13.

Dimethylamine was prepared and tested for possible anodic waves at both pH 4·25 and pH 10·25. No anodic wave was observed before the decomposition potential of the solution. Air was then bubbled through in an attempt to form oxidation products of the amine but, if formed, they yielded no cathodic wave. Potassium permanganate was also added, hydrogen being then passed in until the solution was colourless, but again there was no cathodic wave.

Discussion

Oximes are converted into amines by the action of a variety of reducing agents.[5,6] The results in the present paper will now be discussed, it being assumed that with polarographic reduction also an oxime is converted into the corresponding amine.

The reduction of benzophenone oxime is irreversible since methyldiphenylamine gives no anodic polarographic wave. Also there is no anodic wave produced when benzophenone oxime is hydrogenated *in situ* with palladium–carbon as catalyst.

The cathodic wave found in the pH range 2—6 is probably due to the uptake of four electrons per molecule since the wave height is nearly four times that of the first one-electron wave of the parent ketone in a similar solution; twice that of the two-electron wave in the case of benzoin.[7] The individual factors are: (I), 3·7; (II), 3·5; (III) 4·6; (IV), 3·9; (V), 4·6; (VI), 4·3. In the pH range 2—6 the limiting current is diffusion controlled as shown by its linearity with $H^{1/2}$. In the pH range 6—*ca.* 10 the limiting current becomes independent of H and indicates that the electron transfer is preceded by a reaction the rate of which controls the current.[4]

In equation (1) the oxime is shown in equilibrium with its conjugate acid; HB represents proton donors in the solution, *i.e.*, either buffer weak acid or hydrogen ion and hence its electric charge is not specified.

$$R_2C{:}N{\cdot}OH + HB \rightleftharpoons (R_2C{:}N{\cdot}OH)H^+ + B \quad . \quad . \quad . \quad . \quad . \quad (1)$$

When $(R_2C{:}N{\cdot}OH)H^+$ is removed at the electrode surface by reduction the equilibrium is displaced to the right and continuous protonation of the oxime occurs. With increasing pH the donor HB may be unable to maintain protonation and the reaction becomes slower than the diffusion of oxime to the electrode surface. The decrease in wave height at pH *ca.* 6 is thus explained.

The addition of the four electrons to $(R_2C{:}N{\cdot}OH)H^+$ follows protonation and is probably irreversible since the α values are less than unity.[8,9] To a first approximation the waves are symmetrical. The methods of either Saito [10] or Tanaka and Tamamushi [11] are therefore applied and equation (2) is derived:

$$-E = \text{constant} + (0{\cdot}015/\alpha)\log[i/(i_d - i)] + (0{\cdot}015/\alpha)\log[(h + K_a)/h] \quad . \quad (2)$$

E is the electrode potential, i the current, i_d the limiting current of the wave, h the hydrogen-ion concentration, K_a the dissociation constant of the protonated oxidant, and the coefficient 0·015 is equal to $2{\cdot}303RT/4F$, where R, T, and F are the gas constant, absolute temperature, and faraday, respectively; the coefficient α is regarded by Butler [12] and by

[5] Schöll, *Ber.*, 1927, **60**, 1247.
[6] Kaplansky, *Ber.*, 1927, **60**, 1842.
[7] Gardner, Ph.D. Thesis, Univ. W. Australia, 1954.
[8] Goto and Tachi, *Proc. Intern. Pol. Congr.*, 1951, **1**, 69.
[9] Gardner and Lyons, *Rev. Pure Appl. Chem.*, 1953, **3**, 134.
[10] Saito, *Bull. Soc. chim. France*, 1948, 404.
[11] Tanaka and Tamamushi, *Proc. Intern. Pol. Congr.*, 1951, **1**, 486.
[12] Butler, "Chemical Thermodynamics," Macmillan, London, 1946.

Eyring, Marker, and Kwoh [13] as the fraction of potential assisting the forward reaction (but see also Evans and Hush [14] for an alternative explanation).

Equation (2) gives rise to two predictions by which it may be tested. First, the term $(0{\cdot}015/\alpha)\ \log[i/(i_d - i)]$ becomes equal to zero at $E = E_{\frac{1}{2}}$ ($E_{\frac{1}{2}}$ is the half-wave potential) and hence $E_{\frac{1}{2}}$ should vary with the hydrogen-ion activity as described by the last term of (2). At $pH < pK_a$, $E_{\frac{1}{2}}$ should be pH-independent; at $pH > pK_a$, $E_{\frac{1}{2}}$ should become more negative by $0{\cdot}015/\alpha$ v per pH unit. In the second place α may be calculated from the variation of $E_{\frac{1}{2}}$ with pH and also from the variation of E with $\log [i/(i_d - i)]$. The results for α should agree.

The testing of the first prediction of equation (2) requires a knowledge of pK_a for the conjugate acids of the oximes. The pK_a values are probably about zero since the solubility of the oximes is greatly increased in acid solutions stronger than normal. Therefore in the pH range 2—*ca.* 10, $pH > pK_a$ and in agreement with (2) the measured half-wave potentials are pH-dependent. The condition $pH < pK_a$ for the oximes is not possible in dilute aqueous solutions. However, if the Hammett acidity scale [15] be accepted for reference, then the solvent system sulphuric acid–water provides the condition $H_o < pK_a$ where H_o is the Hammett acidity function. It is found that in fresh solutions of benzophenone oxime in 5—20% sulphuric acid the half-wave potential is nearly constant, in agreement with (2). At higher concentrations of acid the division of the four-electron wave into two waves prevents further test of equation (2).

With methyl *p*-tolyl ketoxime two waves occur at all acid concentrations, each wave being due probably to the uptake of two electrons per molecule. An equation can be derived for two-electron uptake [10] which predicts constancy of $E_{\frac{1}{2}}$ for $pH < pK_a$. In agreement, the half-wave potentials of both waves of methyl *p*-tolyl ketoxime are nearly constant for $H_o < pK_a$.

The second prediction of equation (2) is also largely fulfilled. In Table 3, α is shown at various pH for the lower and upper portions of the wave as α_1 and α_2, respectively. The methods of calculation of α_1, α_2, are from $\alpha_1 = 0{\cdot}0283/n(E_{\frac{1}{2}} - E_{\frac{1}{4}})$ and $\alpha_2 = 0{\cdot}0283/n(E_{\frac{3}{4}} - E_{\frac{1}{2}})$, which quantities are readily derived from equation (2). $E_{\frac{1}{4}}$, $E_{\frac{1}{2}}$, and $E_{\frac{3}{4}}$ represent the potentials at the quarter, half, and three-quarter wave heights, respectively. Also shown are values of α calculated from the pH dependence of the half-wave potential. The agreement between the α values from the above two methods of calculation is moderate with oximes (I), (II), (III), and (VI), and good with (IV) and (V).

The irreversibility of the electron uptake prevents polarographic examination of the subsequent electrode processes. The nature of the protonation which gives the amine must therefore be inferred by analogy with the reduction of carbon–carbon double bonds.[16]

TABLE 3.

Compound	(I)		(II)		(III)		(IV)		(V)		(VI)	
	α_1	α_2	α_1	α_2	α_1	α_2	α_1	α_2	α_1	α_2	α_1	α_2
First wave (pH 2—*ca.* 8) :												
average values of α	0·21	0·30	0·14	0·20	0·23	0·27	0·18	0·21	0·21	0·21	0·14	0·16
α from $E_{\frac{1}{2}}$–pH coefficient	0·19		0·24		0·21		0·21		0·21		0·19	
Second wave (pH > 8) :												
average values of α	0·13	0·13	—	—	0·16	0·16	0·13	—	—	—	—	—

Sodium reduction of 1 : 1-diphenylethylene in liquid ammonia gives negative carbon centres which are highly reactive towards any proton donors present. Hence for the oximes it is suggested that the solvent water is the proton donor and that its reaction with negative nitrogen and oxygen centres is irreversible.

The second wave of benzophenone oxime shows dependence of the wave height upon the pH. The maximum height is nearly equal to that of the first wave, and hence four

[13] Eyring, Marker, and Kwoh, *J. Phys. Colloid Chem.*, 1949, **53**, 1453.
[14] Evans and Hush, *J. Chim. phys.*, 1952, **49**, C159.
[15] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940.
[16] Birch, *Quart. Rev.*, 1950, **4**, 69.

electrons are probably added to each molecule of oxime. The heights of the second waves of methyl β-naphthyl ketoxime and acetophenone oxime are also similar to those of the corresponding first waves. The half-wave potentials are measured with less precision than for the first wave because of the adjacent buffer decomposition current, but within the experimental error they are to be regarded as constant for change in pH.

The electrode processes which give rise to the second wave are probably similar to those for the first wave if the preprotonation is not considered. There would be, first, the irreversible uptake of four electrons by the neutral oxime, followed by irreversible reaction of negative nitrogen and oxygen centres with the aqueous solvent. The half-wave potential is independent of pH since the speed of the protonation reaction depends on the activity of the water, which is present in constant excess, rather than on the hydrogen-ion concentration.

The reaction mechanism of oximes is thus formulated :

(i) Acid pH at pH $>$ pK_a :

$$R_2C{:}N{\cdot}OH + HB \rightleftharpoons (R_2C{:}N{\cdot}OH)H^+ + B^-$$
$$+ 4e \longrightarrow (R_2C{:}N{\cdot}OH)H^{\ddagger}$$
$$+ 3H_2O \longrightarrow R_2CH{\cdot}NH_3^+ + 4OH^-$$

(ii) Alkaline pH :

$$R_2C{:}N{\cdot}OH + 4e \longrightarrow (R_2C{:}N{\cdot}OH)^{\ddagger}$$
$$+ 3H_2O \longrightarrow R_2CH{\cdot}NH_2 + 4OH^-$$

(The symbol ‡ represents an activation state or series of such states, the charge type being unspecified.)

The decrease in height of the second wave of benzophenone oxime in high pH is explicable by dissociation as in equation (3).

$$R_2C{:}N{\cdot}OH \rightleftharpoons R_2C{:}NO^- + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If the rate of recombination is slow, then at pH $>$ pK there will be insufficient $R_2C{:}N{\cdot}OH$ formed at the electrode surface to maintain the maximum limiting current.

The rate of protonation in (i) above depends upon the source of protons HB. It might be expected that at pH $>$ 2 the larger concentration of weak acid molecules than of hydrogen ions would make them the actual proton donors. The rate of protonation would then depend on the nature of HB. However, it is seen from Fig. 2 that when glycine buffers replace the acetic–phosphoric–boric acid mixture the pH of 50% wave height $(pH)_{\frac{1}{2}}$ varies only to a small extent. It is possible therefore that hydrogen ions are the actual proton donors up to pH *ca.* 10. When the formula of Koutecký and Brdička [17] is used together with the estimated pK_a values of zero, and hydrogen ions are assumed to be the actual proton donors, the calculated protonation rate constants would be 10^{14} l. mole^{-1} sec.$^{-1}$.

Experimental

The current–voltage curves were obtained by using Lingane and Kolthoff's three-electrode circuit,[18] with a device for reproducible liquid junctions.[19] The average deviation of four half-wave potentials of benzophenone oxime corrected to pH 2·3 was 3 mv. The average deviation of the limiting currents of five waves at this pH was 1%. A series of saturated calomel electrodes was prepared with the precaution prescribed by Hills and Ives,[20] and their potentials were checked with hydrogen electrodes and with calomel electrodes containing 0·05M-potassium chloride. After they had been used for standards the reference calomel electrode of the polarograph was believed to be 0·242 v against the hydrogen electrode of unit activity at 25°. The polarograms were also taken at 25°, and the half-wave potentials are referred to the above calomel electrode.

[17] Koutecký and Brdička, *Coll. Czech. Chem. Comm.*, 1947, **12**, 337.
[18] Lingane and Kolthoff, *J. Amer. Chem. Soc.*, 1939, **61**, 825.
[19] Gardner and Diamantis, *Austral. J. Sci.*, 1951, **14**, 23.
[20] Hills and Ives, *J.*, 1951, 301.

The ionic strengths in 25% (vol.) ethanol-in-water were calculated by using the apparent pK_a of the buffer acids. These pK_a were determined with a glass electrode and were in agreement with the apparent pK_a expected from the work of Grunwald and Berkowitz.[21]

The buffer solutions were: A, 0·1M each of acetic, phosphoric, and boric acid with sodium hydroxide to the required pH, and potassium chloride added to make $\mu = 0{\cdot}33$; B, Sörensen–Walbaum glycine buffers, with potassium chloride added to make $\mu = 0{\cdot}33$. Solutions contained 25% (vol.) of ethanol. The oximes were prepared by refluxing hydroxylamine with the parent ketone in alcoholic alkali, followed by precipitation with acid. They were identified by m. p. which were (recorded values in parentheses): (I), 143·5° (144°); (II), 153° (153°); (III), 145° (decomp.) (145°); (IV), 59° (59°); (V), 86·5—88° (88°); (VI), 163° (163—164°). On storage several of the oximes decomposed but the solutions in alcohol appeared to be stable. The methyldiphenylamine was prepared by Schöll's method [8] and melted at 186°.

A number of dropping-mercury capillaries were required for the work and hence the diffusion currents are divided by $m^{2/3}t^{1/6}$ where m is the rate of mercury flow (mg. per sec.) and t is the drop time (sec.).

We thank Professor R. J. W. Le Fèvre and Dr. D. P. Mellor for laboratory facilities at the University of Sydney, also Drs. L. E. Lyons and A. Walkley for discussion of this paper.

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[*Received, March 12th*, 1956.]

[21] Grunwald and Berkowitz, *J. Amer. Chem. Soc.*, 1951, **73**, 4939.

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809. *Cytidine Diphosphate Glycerol.*

By J. BADDILEY, J. G. BUCHANAN, A. P. MATHIAS, and A. R. SANDERSON.

One of the cytosine nucleotides isolated from *Lactobacillus arabinosus* has been identified as the cytidine diphosphate glycerol (II). On hydrolysis with dilute acid it yields cytidine-5′ phosphate (I) and α-glycerophosphate (III) with a trace of the β-isomer (IV). These were identified by paper chromatography, by the behaviour of the α-isomer towards periodate, and by enzymic dephosphorylation to glycerol.

When the nucleotide was heated with ammonia the cyclic glycerol phosphate (V) was formed, whereas the venom of *Crotalus atrox* hydrolysed it to cytidine, orthophosphate, and α-glycerophosphate. It is concluded that a pyrophosphate group links cytidine at position 5′ with glycerol in the α-position.*

RECENT improvements [1] in the isolation of the two cytosine nucleotides from extracts of *Lactobacillus arabinosus* [2] have enabled us to obtain purer preparations and consequently more reliable analyses of the ratio base : phosphorus in these substances, and it is clear now that they contain two phosphate residues per cytidine group. In the earlier work it was shown that both are derivatives of cytidine-5′ phosphate (I) and that substituents are probably attached to the phosphate group. We describe here evidence to show that the cytosine nucleotide which is eluted from the ion-exchange column last and which has the higher R_P on paper chromatography in propan-1-ol–ammonia (previously called CPY) is the pyrophosphate (II).

It has become common practice in biochemical work to employ trivial descriptive names for compounds of this general type in which a nucleoside pyrophosphate is esterified

* A preliminary account was published by Baddiley, Buchanan, Carss, Mathias, and Sanderson, *Biochem. J.*, 1956, **63**, 15P.

[1] Baddiley, Buchanan, Carss, Mathias, and Sanderson, *Biochem. J.*, 1956, in the press.

[2] Baddiley and Mathias, *J.*, 1954, 2723.

with some other compound. These names follow the pattern set by Leloir when he used the expression uridine diphosphate glucose (UDPG) for the coenzyme of galactowaldenase. On the same basis the nucleotide derivative (II) can be described as cytidine diphosphate glycerol (CDP glycerol). It must be emphasised, however, that this name, although convenient for many purposes, would not be readily adapted to possible synthetic analogues and that it is therefore important to retain the more systematic pyrophosphate nomenclature for chemical purposes. It is not easy to assign a chemical systematic name which would be applicable also to related compounds and, after consultation with the Editor, we suggest, for temporary use, the name P^1-cytidine-5′ P^2-glycerol-1 pyrophosphate; here the final numeral attached to the name of the polyol denotes the position of the ester group, as in the current nomenclature of nucleotides and the earlier (now abandoned) British nomenclature of carbohydrates.

As only a few milligrams of the compound have been available our evidence relies solely on paper chromatography for the identification of degradation products. The presence of impurities in the preparations could lead to ambiguity in some of the results and in order to overcome this all degradations were carried out on samples which had been run on paper and then eluted. A sample obtained in this way was homogeneous when examined by paper chromatography in several solvent systems. A single spot was observed which absorbed ultraviolet light and gave positive reactions for phosphate [3] and 1 : 2-glycols.[4]

Although the nucleotide is a diphosphate it has a higher R_P in basic solvent systems than has cytidine-5′ phosphate and much higher than cytidine-5′ pyrophosphate (kindly supplied by Dr. J. L. Strominger). This suggests that it contains either fewer acidic groups than cytidine-5′ pyrophosphate or that an additional basic group is present. The latter is unlikely in view of the behaviour of the compound on the Dowex-2 (formate) column. Elution occurs at about the position expected for a cytidine diphosphate : [1] an additional basic group would advance the elution position very considerably.

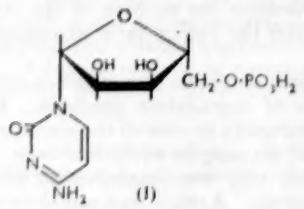
Hydrolysis with N-hydrochloric acid at 100° for 30 minutes and paper-chromatography in propan-1-ol–ammonia afforded two spots with the perchloric acid–molybdate spray reagent [3] for phosphoric esters. The slower-moving spot coincided with an area of absorption of ultraviolet light and corresponded to cytidine-5′ phosphate (I). Full identification of this nucelotide in acid hydrolysates was described earlier.[2] The other phosphoric ester in the hydrolysate could be separated from cytidine-5′ phosphate on a long paper. It did not absorb ultraviolet light but gave a strong reaction for a 1 : 2-glycol when sprayed with periodate followed by Schiff's reagent,[4] the spot developing within a few minutes. This behaviour has been observed with several acyclic glycols, but not with nucleosides and their derivatives which contain a ribofuranosyl structure : with ribofuranosides and other glycosides the colour develops slowly (several hours). The cytosine nucleotide itself rapidly gives a colour which intensifies and deepens somewhat during several hours under the conditions of the test. This suggests that the structure responsible for the rapid appearance of colour in the hydrolysis product is also present in the intact nucleotide. The intensification of colour which occurs later with this substance represents the contribution from the ribofuranose ring in the cytidine residue.

Although the nucleotide-free product of acid hydrolysis ran in propan-1-ol–ammonia as a single spot, in *tert.*-butyl alcohol–picric acid–water it was resolved into a main spot and a faint one with a higher R_P; only the former gave a positive glycol reaction. Further, when the mixture of these two phosphoric esters was eluted from a paper chromatogram, treated with periodate for two hours and then run on paper, the main spot had disappeared and was replaced by one which was indistinguishable from glycollaldehyde phosphate (VI). The faint spot was unchanged by this treatment. These results indicate that the main product from the acid hydrolysis contains the grouping $H_2O_3P{\cdot}O{\cdot}CH_2{\cdot}CH(OH){\cdot}CH(OH)-$. The faint spot would correspond with an isomeric structure $HO{\cdot}CH_2{\cdot}CH(O{\cdot}PO_3H_2){\cdot}CH(OH)-$ which should be stable to periodate :

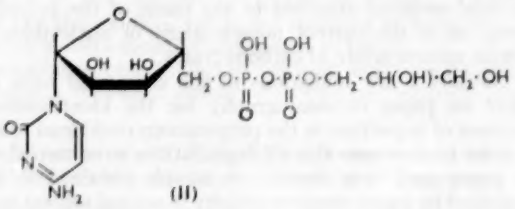
[3] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.
[4] Buchanan, Dekker, and Long, *J.*, 1950, 3162, cf. Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.

this isomer may well have arisen through an acid-catalysed migration of the phosphate group during hydrolysis.

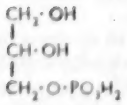
When the nucleotide was hydrolysed with ammonia at 100° for one hour it was partly converted into cytidine-5′ phosphate and a fast-running phosphate which gave no aldehyde with periodate. This new product must be a cyclic phosphate of the structure (V). It had a higher R_P in propan-1-ol–ammonia, and a slower rate of migration on paper electrophoresis at pH 8·7, than had the phosphate formed in the acid hydrolysis. In addition, it was rapidly converted into a mixture of these acyclic phosphates on treatment with acid.



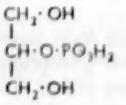
(I)



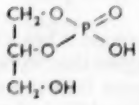
(II)



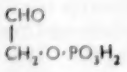
(III)



(IV)



(V)



(VI)

The lability towards acids suggested a 5-membered rather than a 6-membered cyclic phosphate.[5]

The simplest structure for the original nucleotide consistent with these observations is (II). Whereas esters of pyrophosphoric acid are usually stable towards dilute alkali, a hydroxyl group in the adjacent position reduces this stability through the possibility of cyclic phosphate formation. This accounts for the alkali-lability of uridine diphosphate glucose [6] and flavin-adenine dinucleotide.[7] It is interesting that, although the behaviour of the cytosine nucleotide is consistent with structure (II) since it yields a cyclic phosphate on treatment with ammonia, it is more stable in this respect than flavin-adenine dinucleotide or uridine diphosphate glucose. This increased stability is possibly a result of the adoption of a preferred *trans*-configuration of the β-hydroxyl group in the glyceryl residue. The formation of cyclic phosphates under alkaline conditions is probably an intramolecular reaction with steric requirements similar to those of the S_N2 type [8] and consequently would only operate over a narrow range of geometrical possibilities in which the reaction rate would decrease with increase in the angle between the pyrophosphate and the adjacent hydroxyl group. The more vigorous conditions required for acid-catalysed migration of the phosphate group in glycerol phosphates, compared with nucleoside-2′ and -3′ phosphates, may also be due to geometrical factors.

That structure (II) is correct for the nucleotide was shown by a study of the action of phosphatases on the intact substance and on its products of acid hydrolysis, as well as by direct comparison of the phosphates with authentic glycerol phosphates. An acid hydrolysate was run on paper in propan-1-ol–ammonia, and the area corresponding to the non-nucleotide phosphates was cut out, eluted, and hydrolysed by a mixed phosphatase preparation (Polidase-S). The products were identified by paper chromatography as orthophosphate and glycerol. Glycerol was identified by comparison with an authentic

[5] Brown, Magrath, and Todd, *J.*, 1952, 2708; Baddiley and Thain, *J.*, 1951, 3421; Baddiley, Buchanan, and Szabo, *J.*, 1954, 3826.
[6] Paladini and Leloir, *Biochem. J.*, 1952, **51**, 426.
[7] Forrest and Todd, *J.*, 1950, 3295.
[8] Personal communication from Dr. D. M. Brown.

sample in several solvents. It was readily detected by the periodate–Schiff and periodate–benzidine [9] spray reagents and by its weak reaction with silver nitrate.[10]

When the nucleotide was hydrolysed by the phosphatases of *Crotalus atrox* venom the products were cytidine, orthophosphate, and α-glycerophosphate. In this experiment hydrolysis had occurred at the pyrophosphate linkage and also at the nucleoside–phosphate linkage. As no β-glycerophosphate was formed it was concluded that the original nucleotide was a derivative of α-glycerophosphoric acid.

The rapid formation of colour which the intact nucleotide showed in the periodate–Schiff test confirms the α-glycero-structure. In addition, the very small amount of β-glycerophosphate formed on short acid hydrolysis is consistent with an α-structure. The ratio, as estimated on a paper chromatogram, of α- to β-glycerophosphate produced in this way was higher than the equilibrium ratio for these esters which is attained after more vigorous acid treatment. However, the method of analysis is not accurate and these results give no real indication of the mechanism of hydrolysis. When the nucleotide was hydrolysed with sodium hydroxide the products were cytidine-5′ phosphate, β-glycerophosphate, and some α-glycerophosphate. The production of a relatively high proportion of a β-phosphate under these conditions is consistent with structure (II), since α-phosphatides give more β- than α-glycerophosphate under similar alkaline conditions.[11] It has not been established whether the glycerol α-residue has the D- or the L-configuration.

The cyclic phosphate (V) obtained by the action of ammonia on CDP-glycerol was indistinguishable from authentic glycerol 1 : 2-(hydrogen phosphate) [12] both on paper chromatography and on electrophoresis. It was shown that glycerol 1 : 2-(hydrogen phosphate) itself is unaffected by aqueous ammonia at 100° for 60 minutes.

The biochemical function of CDP-glycerol is not yet known. However, its general structure strongly suggests that it is a coenzyme involved in the metabolism of α-glycerophosphate. Since the latter substance is a component of phospholipids it may be that CDP-glycerol is concerned in the condensation of α-glycerophosphate with organic bases such as choline, ethanolamine, and serine, or with fatty acids. It may be significant that another natural derivative of cytidine-5′ pyrophosphate, namely, cytidine diphosphate choline, is concerned with the transfer of a phosphoryl choline molecule in phospholipid biosynthesis.[13]

Experimental

The freeze-dried nucleotide was isolated from a 100 l. batch of bacterial culture by precipitation of nucleotides as mercury salts, ion-exchange chromatography on Dowex-2 (formate) resin, adsorption on charcoal, and elution with aqueous-alcoholic ammonia. Details of this method, and characterisation of the cytidine compound, have been described elsewhere.[1,2] Material obtained in this way was usually homogeneous when examined by paper chromatography but occasionally small amounts of an unidentified adenine nucleotide were detected. This could be removed by dissolving the freeze-dried material in water so that 1 ml. of the solution contained approx. 20 mg. of material and running a suitable quantity on paper in solvent system *B*, cutting out the appropriate area of paper and eluting it with water. In the following experiments the nucleotide was purified in this manner.

Acid Hydrolysis.—(*a*) A sample of nucleotide was hydrolysed for 30 min. at 100° with 6N-hydrochloric acid in a sealed tube. After evaporation in a desiccator *in vacuo*, the hydrolysate was examined by paper chromatography in solvent systems *A*, *B*, and *C* (see below). By comparison with authentic substances run on adjacent tracks the products were identified as cytidine-5′ phosphate, confirmed by its ultraviolet absorption spectrum, and a mixture of α- and β-glycerophosphate in which the α-form predominated. The glycerophosphates were separated from each other in solvent system A.

(*b*) Similar hydrolysis with N-hydrochloric acid effected complete hydrolysis of the pyrophosphate linkage but very little β-glycerophosphate was detected.

Hydrolysis with Sodium Hydroxide.—The nucleotide was hydrolysed in N-sodium hydroxide

[9] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.
[10] Hough, *Nature*, 1950, **165**, 400.
[11] Baer and Kates, *J. Biol. Chem.*, 1948, **175**, 79; Long and Maguire, *Biochem. J.*, 1953, **54**, 612.
[12] Ukita, Bates, and Carter, *J. Biol. Chem.*, 1955, **216**, 867.
[13] Kennedy and Weiss, *J. Amer. Chem. Soc.*, 1955, **77**, 250.

at 100° in a sealed tube for 1 hr. Sodium ions were removed by treatment with a small amount of Dowex-50 (H^+ form) resin, and the solution was examined by paper chromatography in solvent systems *A*, *B*, and *C*. The products were cytidine-5′ phosphate and a mixture of α- and β-glycerophosphate in which the β-form predominated.

Hydrolysis with Ammonia.—The nucleotide was heated with ammonia (*d* 0·880) in a sealed tube at 100° for 1 hr. Hydrolysis was incomplete but the products were identified in solvent system *B* as cytidine-5′ phosphate and glycerol 1 : 2-(hydrogen phosphate). Paper electrophoresis at 200 v in 0·5M-ammonium acetate buffer (pH 8·7) of the phosphate which had been eluted from a paper chromatogram showed its identity with the synthetic material. It moved towards the anode much more slowly than did α- or β-glycerophosphate. The last two substances were not separated from each other.

After hydrolysis of the cyclic phosphate in N-hydrochloric acid for 7 min. at 100° paper chromatography in solvent systems *A* and *B* showed that it was converted into a mixture of glycerophosphates in which the α-form predominated.

Oxidation with Periodate.—The mixture of non-nucleotide phosphates (glycerol phosphates) obtained from an acid hydrolysis of CDP-glycerol was eluted from a paper chromatogram and treated with a slight excess (150 μg.) of sodium metaperiodate in 1·5% solution for 2 hr. at room temperature. Sodium ions were removed by treatment of the solution with a little Dowex-50 (H^+ form) resin, and the products were run on paper in solvent system *A*. The spot corresponding originally to α-glycerophosphate was no longer visible but one which was indistinguishable from glycollaldehyde phosphate was present. The spot corresponding to β-glycerophosphate was unchanged by periodate.

Action of Phosphatases on Glycerophosphates.—Glycerophosphates obtained as described above were treated at pH 7 with an equal volume of a 3% solution of Polidase-S (Schwarz Laboratories, Inc.). This enzyme preparation, which had been dialysed against distilled water at 4° for 4 days, contains several phosphatases including a highly active phosphomonoesterase. After 12 hr. at 37° the mixture was examined by paper chromatography in solvent systems *D*, *E*, and *F*. The products were identified by chromatography as inorganic phosphate and glycerol.

Action of Crotalus atrox *Venom.*—A solution of the nucleotide was treated with a 1% solution of the venom in a glycine–ammonia buffer at pH 9·0 for 12 hr. at 37°. The products were identified by chromatography in solvent system *A* as cytidine, α-glycerophosphate, and inorganic phosphate.

Paper Chromatography.—Unless otherwise stated ascending-front chromatography was carried out on Whatman No. 4 paper which had been washed with dilute acetic acid and water. The following solvent systems were used: *A*, *tert.*-butyl alcohol–picric acid–water (80 ml. : 2 g. : 20 ml.); *B*, propan-1-ol–ammonia–water (6 : 3 : 1); *C*, *iso*butyric acid–ammonia (10 : 6 ml. of 0·5N); *D*, butan-1-ol–acetic acid–water (organic layer) (4 : 1 : 5), *E*, butan-1-ol–ethanol–water (organic layer) (4 : 1 : 5); and *F*, butan-1-ol–benzene–pyridine–water (organic layer) (5 : 1 : 3 : 3). Results are tabulated.

	R_F in solvents						IO_4^-–Schiff reaction
	A •	*B*	*C*	*D*	*E*	*F*	
Cytidine	—	0·61	—	—	—	—	S
CDP-glycerol	0·65	0·31	—	—	—	—	R
α-Glycerophosphate	0·61	0·35	0·37	—	—	—	R
β-Glycerophosphate	0·67	0·37	0·39	—	—	—	O
Cytidine-5′ phosphate	0·38	0·18	—	—	—	—	S
Glycerol 1 : 2-(hydrogen phosphate)	—	0·60	—	—	—	—	O
Glycollaldehyde phosphate	0·42	—	—	—	—	—	S
Glycerol	—	0·74	—	0·54	0·52	0·63	R

S = Slow, R = rapid, O = no reaction; • = descending-front chromatography.

We thank Dr. D. M. Brown for a sample of *Crotalus atrox* venom. This work, which was started at the Lister Institute and continued in Newcastle, was aided by grants from the Department of Scientific and Industrial Research and the Nuffield Foundation. One of us (A. R. S.) thanks the Department of Scientific and Industrial Research for a Maintenance Allowance.

King's College, University of Durham,
Newcastle upon Tyne.

[*Received, April 3rd,* 1956.]

810. *Studies of the Amino-isoquinolines, -cinnolines, and -quinazolines.*

(A) *The Basic Strengths and Ultraviolet Absorption Spectra.*

By A. R. Osborn and K. Schofield.

(B) *The Infrared Spectra.*

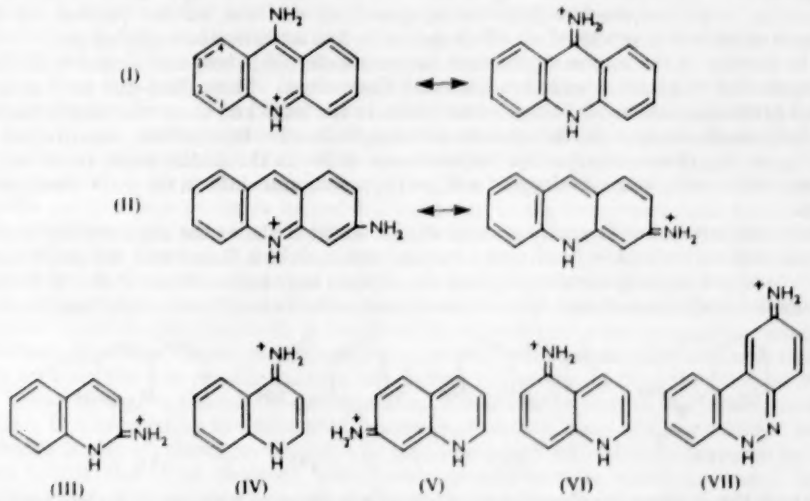
By L. N. Short.

The basic strengths and ultraviolet absorption characteristics of the amino-*iso*quinolines, -cinnolines, and -quinazolines have been determined. The ionisation constants in the first two series can, with minor qualifications, be discussed satisfactorily in terms of the resonance theory, but difficulties arise in the quinazoline group.

The connection between N–H group frequencies and force constants and interaction of the amino-group with the aromatic ring in the above compounds is discussed. Evidence of lack of interaction between $N_{(1)}$ and a 5-amino-group is noted and used to qualify the idea of "additional ionic resonance."

The ultraviolet extinction curves of heteroaromatic amines such as the aminoacridines [1] and aminoquinolines,[2] like those of acridine and quinoline, show in general a marked bathochromic shift when the base is converted into its monocation. This behaviour contrasts with that of typical aromatic amines [3] and proves that in forming monocations the heteroaromatic amines accept the proton on the ring-nitrogen atom.

This information has made possible the rationalisation [4] of the observed basic strengths of a large number of heteroaromatic amines. Thus, the aminoacridines fall into three



groups: those (3- and 4-aminoacridine) of roughly the same basic strength as acridine, those (2- and 5-aminoacridine) considerably stronger than acridine, and an isomer (1-aminoacridine) distinctly weaker than the parent. Base-strengthening is attributed to an

[1] Craig and Short, *J.*, 1945, 419.
[2] Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397.
[3] Harberts, Heertjes, van der Hulst, and Waterman, *Bull. Soc. chim. France*, 1936, **3**, 643; de Borst, Heertjes, van der Hulst, and Waterman, *ibid.*, 1938, **70**, 3397.
[4] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

" additional ionic resonance effect " (see I and II) (a similar situation, formally possible in 4-aminoacridine, would involve less stable *o*-quinonoid forms: but see Short [5] and Discussion below). Infrared studies [5] suggest that base-weakening in the 1-isomer is due to intramolecular hydrogen bonding.

Gore and Phillips,[6] seeking regularities in ΔpK_a (the difference between pK_a for the amine and for the parent base), classified the possible ionic structures as *ortho*-quinonoid, *e.g.*, (III), *para*-quinonoid (IV), *ortho-para*-quinonoid (V), *ortho-ortho*-quinonoid (VI), and *para-para*-quinonoid [their only available example being " 2-aminobenzocinnolinium," the benzocinnolinylideneammonium compound (VII)]. They concluded " that the ΔpK_a associated with any particular quinonoidal structure is reasonably constant for several heterocyclic nuclei," and on this premise predicted pK_a values for the three " *para-para* "-types: 6-amino-*iso*quinoline, -phthalazine, and -phenanthridine.

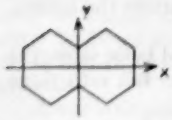
Our present aim was further to test the various ideas mentioned above by examining the amino*iso*quinolines, and then to investigate the use of pK_a and spectroscopic studies in throwing light on the problem of the basic centre in diazines, especially the amino-cinnolines and -quinazolines.

Discussion

(A) *Basic strengths and ultraviolet absorption spectra.*

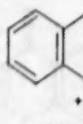
Results are summarised in Tables 1 and 2.

(a) iso*Quinolines.*—The assignment by Lewis and Calvin [7] of the three main absorption bands in the spectrum of naphthalene (310, 280—260, 220 mμ) to electronic transitions polarised parallel to (x), parallel to (y), and parallel to (x) respectively, received support from Kiss's work [8] on the effect of substituents upon these bands. Tombacz [9] related the three main bands in the *iso*quinoline spectrum to those of naphthalene, and indicated that the bathochromic displacement of the long-wavelength band observed in *iso*quinoline (but not in quinoline) was due to the position of the nitrogen atom which produced an effect similar to β-substitution in naphthalene.

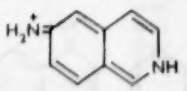


The spectra of the amino*iso*quinolines (neutral molecules) show shifts relative to that of *iso*quinoline which are roughly in accord with these views. Thus, the 3- and the 7-amino-groups produce considerable bathochromic shifts in the long- and short-wavelength bands, but only small changes in the medium-wavelength band. In contrast, substitution at $C_{(1)}$, $C_{(4)}$, or $C_{(8)}$ causes considerable bathochromic shifts in the middle band, small bathochromic shifts in the long-wavelength band, and hypsochromic shifts in the short-wavelength band.

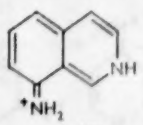
8-Amino*iso*quinoline is partly anomalous, for whilst it shows the expected big bathochromic shift in the middle band, and a hypsochromic effect is found with the short-wavelength band, yet the long-wavelength band also shows a large bathochromic shift. 6-Amino-*iso*quinoline is also anomalous: here all three bands suffer bathochromic shifts, considerable



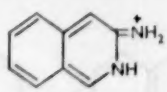
(VIII)



(IX)



(X)



(XI)

only with the medium-wavelength one; further, a decrease in intensity is noticed with the short-wavelength band, and an increase with the middle band.

In solutions sufficiently acid to convert them into monocations all the amino*iso*quinolines show bathochromic shifts of their ultraviolet extinction curves. Following Craig and

[5] Short, *J.*, 1952, **4584**.
[6] Gore and Phillips, *Nature*, 1949, **163**, 690.
[7] Calvin and Lewis, *Chem. Rev.*, 1939, **25**, 273.
[8] Kiss, *Compt. rend.*, 1949, **229**, 762.
[9] Tombácz, *Magyar Kém. Folyóirat*, 1950, **56**, 175.

Short [1] we take this to indicate that the amines accept the first protons on their ring-nitrogen atoms.

This conclusion, together with Albert's idea of additional ionic resonance, makes it possible to rationalise the ΔpK_a values observed for the amino*iso*quinolines (Table 2). Thus amines with monocations from which additional ionic resonance is absent (4-, 5-, and 7-amino*iso*quinolinium) give values for ΔpK_a smaller than 1 unit. In contrast, 1-, 6-, and 8-amino*iso*quinoline [cations (VIII), (IX), and (X)] give ΔpK_a values considerably greater than 1 unit. 6-Amino*iso*quinoline thus parallels 7-aminoquinoline.[4] The case of 3-amino*iso*quinoline is particularly interesting. If the evidence of the ultraviolet absorption spectra is accepted as indicating that this amine receives its first proton on the ring-nitrogen atom, then the *ortho*-quinonoid ionic resonance form (XI) clearly does not increase the stability of the cation relative to that of the free base. Presumably the destruction of conjugation between the nucleus and the amino-group which would result from cationisation of the latter is even less favourable energetically. Infrared examination (see below) shows the amine itself to be normal.

Apart from the case of 8-aminoquinoline, where intramolecular hydrogen bonding is important, negative values of ΔpK_a have hitherto been observed only with 4- and 7-aminopteridine,[10] derivatives of a heterocyclic nucleus with a much higher N : C ratio than has *iso*quinoline. Further reference will be made to this point below.

(b) *Cinnolines.*—The absorption spectrum of cinnoline in *cyclo*hexane [11] differs from that of, say, *iso*quinoline [12] in showing a further low-intensity band (log $\varepsilon_{max.}$ 2·42) at 390 mμ. We discuss the effect of substituents on this band in an accompanying paper but it may be noticed here that its disappearance from the spectrum of cinnoline in water or acid (Table 1) is in keeping with its origin in an $n \longrightarrow \pi$ transition.[13]

In the aminocinnolines the conjugation of the substituent with the heterocyclic nucleus generally causes such considerable modification of the absorption spectrum that even the degree of regularity observed with the *iso*quinolines is not discernible here. The band due to the $n \longrightarrow \pi$ transition is of course obscured, and the spectra of the neutral molecules in aqueous solutions all show large bathochromic shifts of the first long-wavelength band, as compared with cinnoline. The magnitude of the shift decreases in the order 8- > 7-, 5-, 3- > 6- > 4, which, except for the position of the 8-isomer, is roughly that observed with the *iso*quinolines. The bathochromic shifts of the middle band decrease in the order 5-, 8- > 4- > 3-, with 7-aminocinnoline possibly showing a slight hypsochromic effect. The order is that expected if the band is connected with polarisations along the short axis of the molecule. As in the *iso*quinoline series, the 6-isomer is anomalous. Conversion into the monocations produces further bathochromy in the long-wavelength band in all cases (solutions containing the monocations of 5- or 8-aminocinnoline are violet-red, solutions containing those of 6- and 7-aminocinnoline are yellow). Again, this is taken to indicate that in the monocations the protons are attached to ring-nitrogen atoms.

In attempting to use this evidence from absorption spectra, in conjunction with the observed values of ΔpK_a (Table 2), to decide which ring-nitrogen atom in an aminocinnoline is the basic centre we should perhaps state that we realise that an equilibrium must always exist between the two possible cations, one having the proton at $N_{(1)}$, the other at $N_{(2)}$. By "basic centre," we mean the nitrogen atom which acts as such in the predominating cation. It is interesting to notice that 6-aminoquinolinium, from which additional ionic resonance is absent, shows an elevation in pK_a (compared with quinolinium) smaller by about 1 unit than that observed with 7-aminoquinolinium, in which additional ionic resonance first becomes important. A similar or larger difference exists between the values for 7-amino*iso*quinolinium (no additional ionic resonance) and 6-amino*iso*quinolinium, and between 5-aminocinnolinium (for which the resonance theory would postulate the unfavourable *ortho-ortho*-quinonoid form) and 8-aminocinnolinium, the member of the series

[10] Albert, Brown, and Cheeseman, *J.*, 1951, 474; Albert, Brown, and Wood, *J.*, 1954, 3832.
[11] Hearn, Morton, and Simpson, *J.*, 1951, 3318.
[12] Friedel and Orchin, "Ultra-violet Spectra of Aromatic Compounds," Wiley and Sons, New York, London, 1951.
[13] (*a*) Mason, "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," *Chem. Soc. Special Publ.*, No. 3, 1955, p. 139; (*b*) Badger and Walker, *J.*, 1956, 122.

TABLE 1.

Substance	Ionisation (H_2O; 20°) pK_a	Concn.	Spectroscopy (in water). $\lambda_{max.}$ (mμ) ($\log_{10} \varepsilon_{max.}$)	pH
*iso*Quinoline	5·40 ± 0·01 [a]	316	319(3·47) + 306(3·38); 278 [b] (3·41) + 267(3·57); 216(4·81)	9·22
			332(3·63); 273(3·31) + 266(3·30); 227(4·66)	2·0
*iso*Quinoline methochloride	—	—	336(3·62) + 330 [b] (3·61); 287 [c] (3·12) + 277(3·41) + 269(3·40); 231(4·70)	*ca.* 7·0
3-Aminoisoquinoline	—	—	353(3·42); 288 [b] (3·58) + 278(3·73) + 269(3·67); 231(4·74)	9·21
	5·05 ± 0·01	400	390(3·62); 296(3·21) + 285(3·52) + 277(3·53); 237(4·76)	2·54
4- ,,	—	—	332(3·74); 310 [b] (3·64); 248 [c] (3·94) + 240 [b] (4·10); 210(4·68)	9·21
	6·28 ± 0·01	400	354(3·94); 316 [b] (3·55); 262 [c] (3·59) + 238 [c] (4·07); 217(4·50)	3·28
5- ,,	—	—	332(3·70); 238(4·22); 205(4·48)	9·21
	5·59 ± 0·01	400	378(3·53) + 340(3·53); 259(4·18); 208(4·56)	3·07
6- ,,	—	—	326 [b] (3·47); 304(3·84) + 296(3·83); 239(4·61) + 234(4·60)	9·21
	7·17 ± 0·04	1000	352(4·03) + 337(4·01); 266(4·32); 238 [b] (4·34) + 231(4·43)	4·27
7- ,,	—	—	349(3·40); 273(3·90); 231(4·56)	9·21
	6·20 ± 0·02	1000	385(3·35); 289(3·82); 254(4·58); 218(4·14)	3·22
8- ,,	—	—	345(3·68) + 307 [c] (3·51); 224 [c] (4·36); 207(4·61)	9·21
	6·06 ± 0·01	400	417(3·66) + 325(3·41); 250(4·26); 209(4·54)	3·05
Cinnoline	—	—	321(3·44); 290(3·38) + 283(3·38); 226(4·64)	7·0
	2·29 ± 0·03 [d]	225	353(3·40); 305(3·32) + 294(3·31); 237(4·59)	0·3
Cinnoline methochloride	—	—	357(3·43); 308(3·46) + 296(3·47); 241(4·64)	*ca.* 7·0
4-Methylcinnoline	—	—	330 [c] (3·47) + 320(3·54) + 308 [c] (3·42); 292(3·52) + 283(3·50); 225(4·68)	7·0
	—	—	349(3·52); 306(3·44) + 300 [b] (3·40); 235(4·58)	0·3
4-Methylcinnoline methochloride	—	—	354(3·57); 308(3·49) + 297(3·49); 239(4·63)	*ca.* 7·0
3-Aminocinnoline [e]	—	—	374(3·44); 304 [c] (2·93) + 283 [c] (3·29); 234(4·61); 211(4·30)	7·0
	3·70 ± 0·03	1000	405(3·47); 327(2·71) + 314(2·87); 237(4·61); 211(4·08)	2·02
4- ,, [f]	—	—	338(4·03) + 310 [c] (3·71); 255 [c] (3·77); 238(4·18); 212(4·52)	9·21
	6·85 ± 0·04	400	360 [b] (4·03) + 345(4·12) + 295(3·24); 262(3·83); 236(4·16); 211(4·45)	4·35
5- ,,	—	—	382(3·34); 334(3·28); 254(4·36) + 235 [c] (4·14)	7·0
	2·70 ± 0·06	1000	490(3·00); 348(3·32); 280(4·00)236(4·25)	0·3
6- ,,	—	—	362(3·74); 315(3·58); 256(4·50); 206(4·36)	9·22
	5·04 ± 0·04	1000	416(4·02); 338(3·47) + 326(3·51); 276(4·34); 220(4·36)	2·02
7- ,,	—	—	385(3·43); 283(3·77); 249(4·60); 206(4·43)	9·22
	4·85 ± 0·01	400	446(3·67); 318 [c] (3·23) + 292 [c] (3·63); 268(4·61); 210(4·36)	2·02
8- ,,	—	—	395(3·40); 327(3·21); 251(4·41)	9·22
	3·68 ± 0·01	400	520(3·48); 344(3·44); 260(4·22) + 245 [b] (4·18)	0·3
Quinazoline [g]	—	—	306(3·38); 272(3·41); 222(·458)	7·0
	3·51 ± 0·01	277	259(3·94); 207(4·27)	1·0
Quinazoline methochloride	—	—	265(3·92)	0·3

2-Aminoquinazoline [b]	—	—	352(3·50);	259[c] (3·75);	246[c] (4·32) + 233(4·57)	9·20
	4·82 ± 0·03	1000	348(3·49) + 339[b] (3·45);	284(3·72)	245(4·26) + 229(4·41)	2·02
4- ,, [d]	—	—	323(3·65) + 312(3·78) + 300[c] (3·66);	283(3·82) + 278[b] (3·81);	228[b] (4·18) + 214[c] (4·38) + 206(4·52)	9·21
	5·85 ± 0·06	1000	324(3·87) + 311(3·98) + 303[c] (3·87);	284(3·62) + 273(3·58);	252[c] (3·99) + 238(4·13)217(4·26)	2·87
5- ,,	—	—	372(3·45) + 336[b] (3·32);	249(4·55); 206(4·26)		9·20
	3·57 ± 0·01	1000	462(2·72)305(3·40);	260[b] (4·03) + 245(4·09)		2·02
6- ,,	—	—	360(3·42);	277(3·70);	242(4·54); 207(4·31)	7·0
	3·29 ± 0·02	1000	310[c] (2·70);	260(3·98); 208(4·26)		1·7
7- ,,	—	—	345(3·80);	293(3·73); 251(4·48);	228[b] (4·32); 204(4·37)	9·20
	4·60 ± 0·03	1000	373(4·06);	328(3·71); 270(3·32);	231(4·21); 213(4·35)	2·02
8- ,,	—	—	338(3·46);	238(4·42)		7·0
	2·81 ± 0·03	1000	415(2·52); 310(3·23);	265(3·90); 215(4·28)		1·07
6-Chloroquinazoline	—	—	325(3·32) + 316(3·36);	263(3·50); 227(4·68)		7·0
	—	—	265(4·02); 208(4·22)			0·3
5-Aminoquinoxaline	—	—	380(3·14); 330(3·20) + 322(3·21);	261(4·39); 230(3·76); 207(4·04)		7·0
	—	—	313(3·72); 290[c] (3·58);	233(4·44); 207(4·15)		0·0
6- ,,	—	—	372(3·74); 286[c] (3·40);	254(4·42); 207(4·46)		7·0
	—	—	358(3·82); 322[b] (3·38);	270(4·34); 232(3·92) + 214(4·33)		0·3
Phenanthridine	—	—	346(3·24); 330(3·26);	296[c] (3·75) + 290(3·79);	268[c] (3·99); 247(4·66); 216[c] (4·36) + 209(4·40)	9·21
	4·52 ± 0·01 [h]	—	366(3·45) + 345(3·48);	315(3·79); 247(4·62); 218(4·12)		2·01
	—	—	365[b] (3·56) + 357(3·57);	322[b] (3·86) + 316(3·89);	247(4·13); 207(4·38)	0·0
6-Aminophenanthridine	6·88 ± 0·02 [i]	—	321(4·13);	278[c] (3·94);	251(4·63) + 223[c] (4·27)	9·22
Quinoline methochloride	—	—	316(3·89) + 308[c] (3·85);	237(4·56)		*ca.* 7·0

[a] Kolthoff (*Biochem. Z.*, 1925, **162**, 289) gave 5·14. Albert (*Chem. Soc. Special Publ.* No. 3, 1955, p. 138) gave 5·46. [b] Shoulder. [c] Inflexion. [d] Albert *et al.*[4] gave 2·70. [e] Alford and Schofield (*J.*, 1953, 1811) gave 3·63. [f] Albert *et al.*[4] gave 6·84. [g] Albert *et al.*[4] gave 3·51. [h] Albert *et al.*[4] gave 4·43. A new determination by Professor Albert (personal communication) gave 4·78. [i] Albert *et al.*[4] gave 5·73. [j] Elderfield *et al.* (*J. Org. Chem.*, 1947, **12**, 405) gave 3·2 and 2·4 (in 50% ethanol) for 6- and 8-aminoquinazoline respectively. [k] Isosbestic point 301 mμ, $\log_{10}\varepsilon$ 3·71; Albert *et al.*[4] gave pK_a 3·30 in aqueous ethanol. [l] Curves at pH 9·22, 7·52, 6·35, and 4·0 gave an isosbestic point at 341 mμ, $\log_{10}\varepsilon$ 3·89.

TABLE 2. ΔpK_a *values.*[a]

Aminoquinoline		Aminoisoquinoline		Aminocinnoline		Aminoquinazoline	
NH_2	ΔpK_a	NH_2	ΔpK_a	NH_2	ΔpK_a	NH_2	ΔpK_a
2-	2·40	1-	2·22	3-	1·41	2-	1·31
3-	0·01	3-	−0·35	4-	4·56	4-	2·34
4-	4·23	4-	0·88	5-	0·41	5-	0·06
5-	0·52	5-	0·19	6-	2·75	6-	−0·22
6-	0·69	6-	1·77	7-	2·56	7-	1·09
7-	1·71	7-	0·80	8-	1·39	8-	−0·70
8-	−0·95	8-	1·66				
		6-Aminophenanthridine	2·36				

[a] The figures for aminoquinolines and 1-aminoisoquinoline are from Albert, Goldacre, and Phillips.[4]

least favoured by additional ionic resonance. It does not seem unreasonable, therefore, to suppose that in an amino-compound containing two ring-nitrogen atoms, even in unfavourable circumstances the nitrogen atom capable of taking part in additional ionic resonance would be the predominantly cation-forming one (a difference in pK_a of 1 unit producing 90% of the preferred species).

The ultraviolet extinction curve for cinnoline cation at pH 0·3 (Fig. 1) is very similar to that for "cinnoline methochloride" prepared from the methiodide as described in the Experimental section. The slight bathochromic and hypsochromic differences are very similar to those between *iso*quinoline cation at pH 2·0 and *iso*quinoline methochloride (Table 1), and both sets of curves are very different from those for quinolinium and *N*-methylquinolinium (Table 1). This situation is unexpected, for Atkinson and Taylor [14]

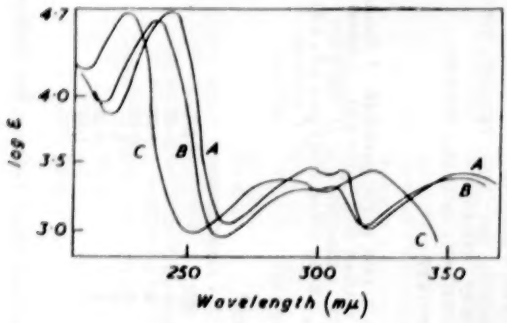


FIG. 1. *A, Cinnoline methochloride; B, cinnoline cation* (pH 0·3); *C, cinnoline* (pH 7).

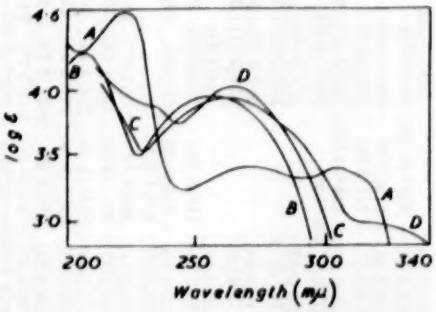


FIG. 2. *A, Quinazoline* (pH 7); *B, quinazoline cation* (pH 1·0); *C, quinazoline methochloride* (pH 0·3); *D, quinazoline methohydroxide* (pH 7).

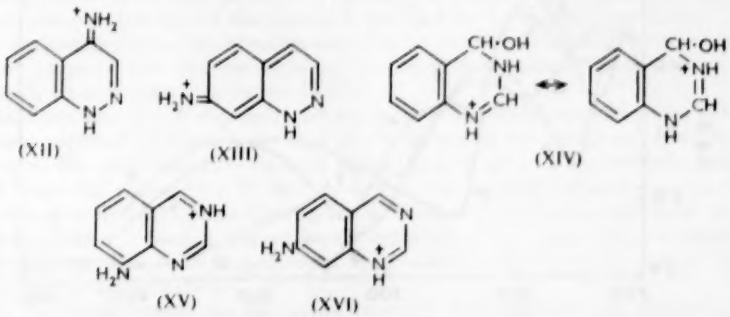
recently concluded from degradative studies that methyl iodide reacts with cinnoline at $N_{(1)}$. Nevertheless, without evidence of spectroscopic differences, if any, between unambiguously constituted $N_{(1)}$- and $N_{(2)}$-methylcinnolinium salts, the possibility remains that the extinction curve for cinnoline in acid is that of a mixture of cations.

With the aminocinnolines the situation is generally much clearer. Thus, for 4-aminocinnoline the large ΔpK_a value must indicate that $N_{(1)}$ is the basic centre,[4] the cation (XII) being highly stabilised. The resonance theory would predict a low value of ΔpK_a for 5-aminocinnoline, the only cationic form which could possess additional ionic resonance being the unfavourable *ortho-ortho*-quinonoid one analogous to (VI). A low value of ΔpK_a is found, but there is evidence (see below) of peculiarity in the structure of the free base itself. $N_{(1)}$ is presumably the more favoured basic centre, but a clear-cut choice cannot be made. The monocation of 6-aminocinnoline is clearly much stabilised, and the ΔpK_a value is readily understood if $N_{(2)}$ is the basic centre, the case being analogous to that of 6-amino*iso*quinoline (cf. IX). Similarly, 7-aminocinnoline must be analogous to 7-aminoquinoline, with the basic centre now shifted to $N_{(1)}$ (XIII). 8-Aminocinnoline is

[14] Atkinson and Taylor, *J.*, 1955, 4236.

interesting since in it the effect of intramolecular hydrogen-bonding (see below), which in 8-aminoquinoline results in a negative ΔpK_a, has been avoided by cation formation at $N_{(2)}$. This suggestion is strengthened by the similarity of the ultraviolet extinction curves of 8-aminocinnoline and 8-amino*iso*quinoline, and by the way in which those curves change on cation formation. From earlier measurements which gave $\Delta pK_a \sim 1$ for 3-aminocinnoline, Alford and Schofield [15] concluded that in this compound $N_{(2)}$ is the basic centre. The somewhat higher value of ΔpK_a now observed strengthens this conclusion. However, the compound contrasts strongly with 3-amino*iso*quinoline. In the cations of both *ortho-ortho*-quinonoid forms are involved, and the differing values of ΔpK_a show the difficulty of attaching significance to the absolute value of this quantity (see below).

(c) *Quinazolines.*—The ultraviolet extinction curve of the neutral quinazoline molecule (Fig. 2) exhibits the three main bands characteristic of such bicyclic systems, and appears to be in no way abnormal. Surprisingly, however, the extinction curve of the cation shows marked hypsochromy, and above 200 mμ only two bands remain, both of high intensity. The more usual effect, observed with the cations of quinoline,[10] *iso*quinoline, cinnoline, pteridine,[10] acridine,[16] and the diazines,[17] is a slight bathochromic shift. (The extinction curve for pyridine is substantially unchanged on cationisation.) There is at present no evidence to suggest that the behaviour of quinazoline is due to any disruptive change in acid solution. If ring-opening were occurring, a slow movement to equilibrium might be evident on titration of quinazoline with acid. This is not observed. Nor is the possibility, mentioned to us by Professor A. Albert, that quinazoline exists in aqueous solution in a form having water added to the 3 : 4-double bond in agreement with the normal extinction curve of the neutral molecule, or with the tendency for the extinction curve of 3-methylquinazolinium (Fig. 2) to move, at higher pH values, away from the quinazoline spectrum. The alternative possibility that the quinazoline *cation* is in the same sense hydrated [18] cannot at present be excluded, although the properties of *pseudo*-bases derived from quaternary heteroaromatic salts [19] would make stability in acid solution a surprising attribute of such a cation were it not for the new possibilities of resonance stabilisation in such a structure (XIV). Nevertheless, Gabriel and Colman [20] observed that



(XII) (XIII) (XIV)

(XV) (XVI)

3-methylquinazolinium iodide when recrystallised from methanol could not be freed from one molar equivalent of the latter without causing decomposition, and Schöpf and Oechler [21] encountered similar difficulties in freeing 3-methyl- and 3-allyl-quinazolinium picrate from ethanol. For these reasons, and because the cationic spectrum of quinazoline points to a modification of the aromatic system, we shall assume as a working hypothesis that the quinazoline cation should be represented as the resonance-stabilised hydrated form (XIV).

[15] Alford and Schofield, *J.*, 1953, 1811.
[16] Albert, "The Acridines," Arnold, London, 1951.
[17] Halverson and Hirt, *J. Chem. Phys.*, 1951, **19**, 711.
[18] Albert, see ref. 13*a*, p. 138.
[19] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 575.
[20] Gabriel and Colman, *Ber.*, 1904, **37**, 3643.
[21] Schöpf and Oechler, *Annalen*, 1936, **523**, 1.

In the first place we have looked for other examples of this type of behaviour. Irving and Rossotti [22] have recorded the hypsochromy produced in the spectrum of 8-hydroxyquinazoline by cationisation and we found similar changes for 6-chloroquinazoline and 6 : 7-benzoquinazoline. Dr. S. F. Mason (personal communication) found the same to be true of 2-methylquinazoline, but between 4-methylquinazoline and its cation (as also with 8-hydroxy-2 : 4-dimethylquinazoline [22]) the more usual bathochromic relation exists. The extinction curve of "3-methylquinazolinium" (Fig. 2) resembles very closely that of quinazoline cation, showing the expected small bathochromic shift. In this case, as in the others quoted, we should, in terms of the working hypothesis, regard the cation as

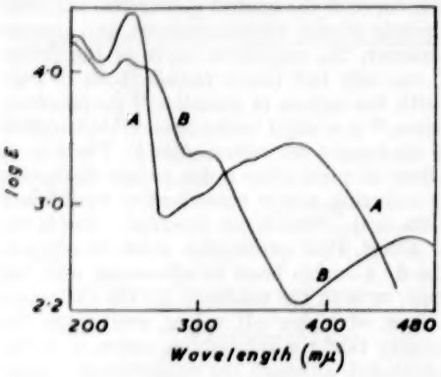
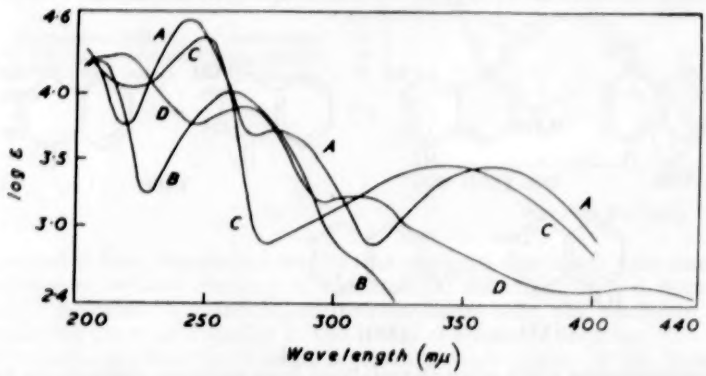


FIG. 3. *A, 5-Aminoquinazoline* (pH 9·20); *B, 5-aminoquinazoline cation* (pH 2·02).

FIG. 4. *A, 6-Aminoquinazoline* (pH 7); *B, 6-aminoquinazoline cation* (pH 1·7); *C, 8-aminoquinazoline* (pH 7); *D, 8-aminoquinazoline cation* (pH 1·07).



having a structure of the type (XIV) (Me instead of H at $N_{(3)}$), whilst 4-methyl- and 8-hydroxy-2 : 4-dimethyl-quinazoline presumably form cations without hydration. Only in such cases as these last two is it meaningful to enquire whether $N_{(1)}$ or $N_{(3)}$ is the basic centre.

The extinction curves of the neutral molecules of all the aminoquinazolines show in the long-wavelength bands the expected bathochromic shift relative to quinazoline, but are not amenable to further rationalisation. With regard to the behaviour of their extinction curves upon cationisation, the amines fall into three groups. Thus, with 4-aminoquinazoline the long-wavelength band is substantially stationary (though showing increased

[22] Irving and Rossotti, *J.*, 1954, 2910.

intensity), whilst 2-aminoquinazoline shows only slight hypsochromy. The two compounds recall the behaviour of 4- and 2-aminoquinoline.[2] In contrast marked hypsochromy results from cationisation of 6-aminoquinazoline (Fig. 4) and, finally, cationisation of 5- (Fig. 3), 7-, and 8-aminoquinazoline (Fig. 4) produces the more more familiar bathochromy, though intensity changes are not similar in all three cases. Pursuing the argument outlined above, and bearing in mind the similarity to the quinoline series, we assume further that 2- and 4-aminoquinazoline are compounds which are not hydrated on cationisation. The same appears to be true of the 5-, 7-, and 8-isomers, but 6-aminoquinazoline is presumably hydrated.

It is necessary to see how far these tentative deductions fall in with the evidence from ΔpK_a values (Table 2). Phillips (quoted by Albert [23]) considered $N_{(3)}$ to be the basic centre in 4-aminoquinazoline since the amino-group produces "too little exaltation of basic strength over quinazoline to be γ to the basic nitrogen atom." It seems to us, in view of the quantity of evidence now available (see below also), that the idea of a ΔpK_a value's being fairly constant from series to series and associated with a particular quinonoid structure cannot be generally sustained. For this reason we cannot attach much weight to the argument, especially in the present instance, where the pK_a of the reference compound (quinazoline) may be that of a modified structure (XIV). In this connection it has been observed [24] that quinazoline appears to be a stronger base than expected, a fact which is understandable if the quinazoline cation does in fact possess a structure such as (XIV). It is known [25] that 3 : 4-dihydroquinazolines are much stronger bases than quinazolines, and reference of 4-aminoquinazoline to a structure such as (XIV) would give too small a value for ΔpK_a. It should also be noted that derivatives of 4-aminoquinazoline are known [26] to quaternise at $N_{(1)}$. The balance of evidence thus appears to favour $N_{(1)}$ as the basic centre in 4-aminoquinazoline.

Comments on the neutral molecules of 5- and 8-aminoquinazoline will be found below, but the difficulty of attaching real significance to ΔpK_a values in the quinazoline series makes impossible a choice of basic centres in these cases. The considerable negative ΔpK_a value found for 8-aminoquinazoline might arise from the lack of stabilisation in the cation (XV) and the elevated basic strength of quinazoline rather than from the adoption of $N_{(1)}$ as basic centre in the face of the chelation revealed by the infrared spectrum. However, with 7-aminoquinazoline the situation seems to be clear-cut. As stated, the spectroscopic evidence suggests that the cation is normal, and the relatively large ΔpK_a value can confidently be referred to the cation (XVI).

6-Aminoquinazoline is especially interesting. The ultraviolet extinction curve might have been expected to throw some light on the nature of the cation and so reveal the significance of the small negative value of ΔpK_a (in 50% ethanol 6-aminoquinazoline is not weaker than the parent [25]). In fact, however, the marked hypsochromy produced by cationisation of 6-aminoquinazoline results in a curve very closely similar to that of the quinazoline *cation*! Such a change would ordinarily occur only if the amine had taken up two protons, one on a ring-nitrogen atom and one on the amino-group. This case requires further investigation.

It is clear from present and previously available data that the basic strength of heteroaromatic amines can to a large degree be rationalised by resonance theory, qualified in some cases by the effects of chelation, and in others, where a *peri*-amino-group is in question (see below), by the recognition that abnormalities are to be referred to the amine molecule rather than its cation. Other considerations enter the argument in cases where a 1 : 3-diazine system is present, permitting modification of the aromatic system in the cation whilst still allowing a considerable degree of resonance stabilisation. Such a case is presented by the quinazolines discussed here, and by the pteridines.[10] The observation that 4-methylquinazoline and 4-methylpteridine are weaker bases than their parents [10] is understandable if, for reasons discussed above, the parents seem to be too strongly basic.

[23] Albert, *Quart. Rev.*, 1952, **6**, 202.
[24] Schofield, see ref. 13*a*, p. 137.
[25] Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405.
[26] Morley and Simpson, *J.*, 1948, 360.

We propose to study further derivatives of quinazoline and 3 : 4-dihydroquinazoline in pursuit of support for these ideas.

In another diazine series, the quinoxalines, the relative basic strengths of the parent and the amines [4] are understandable, and cationisation of quinoxaline [10] produces the familiar small bathochromic shift in the extinction curve. We find (Table 1) that 6-aminoquinoxaline also follows the usual pattern, but that 5-aminoquinoxaline gives upon cationisation a curve which shows marked hypsochromy and only two bands. In contrast to the case of 6-aminoquinazoline, however, this curve is closely similar to that of quinoxaline,[10] and 5-aminoquinoxaline appears to be the first example of a heteroaromatic amine which takes up the first proton on its amino-group.

(d) para-para-*Quinonoid Systems*.—The compounds examined in this work which belong to this category are 6-amino-*iso*quinoline, -cinnoline, and -phenanthridine (pK_a 7·17, 5·04, and 6·88; ΔpK_a 1·77, 2·75, and 2·36 respectively). The constancy of ΔpK_a among a group of miscellaneously derived amines, related only by the formal similarity of their cations,[6] cannot be maintained with any accuracy. These figures show however that "2-aminobenzocinnoline" (pK_a 6·68, ΔpK_a 4·48) [6] is a much stronger base than would be expected, and support Calderbank and Le Fèvre's observations [27] in throwing doubt on the structure of this compound.

B. *Infrared spectra.*

In a previous paper [5] it was shown that the N–H bond-stretching frequencies of the monoamino-acridines and -quinolines could be interpreted in terms of the electromeric effect produced by the ring-nitrogen atom. In general, for those positions of the amino-group for which interaction with the ring-nitrogen atom is possible, the N–H group frequencies and corresponding force constants were found to be significantly higher and to parallel values calculated for the extra electron density on the ring-nitrogen atom. The N–H force constants in these groups of isomeric heteroaromatic amines indicate the extent to which the amino-group interacts with the aromatic ring and increases the electron density at the ring-nitrogen atom. The N–H bond-stretching frequencies of the amino-*iso*quinolines, -cinnolines, and -quinazolines have now been determined, and along with those for the aminopyrimidines and 5-aminoquinoline (kindly supplied by Dr. D. J. Brown and Mr. A. Bryson respectively) are collected in Table 3. The force constants were calculated as previously described.[5]

It seems reasonable to expect electromeric interaction to occur in those cases for which it is formally possible. In the *iso*quinoline series this would apply to 3-, 6-, and 8-amino-*iso*quinoline.

It is seen, however, that the force constant for 8-amino*iso*quinoline is only very slightly higher than that of the 7-isomer, while 3- and 6-amino*iso*quinoline give significantly higher values. In the quinoline series the 2-, 4-, 5-, and 7-isomers should give high values but the force constant for 5-aminoquinoline is almost equal to that of 3-aminoquinoline and 4-aminoacridine (6·55, 6·54, and 6·55 $\times$ 10^5 dyne cm.$^{-1}$ respectively). These results find no explanation in the published electron-density calculations.[28]

Some doubt is thrown on the "extra ionic resonance" explanation [4] of such facts as the low pK_a value of 4-aminoacridine relative to that of acridine, namely, that it is due to the instability of the *o*-quinonoid forms. Since 4-aminoacridine has an anomalous N–H force constant, the lowest for the aminoacridines, the abnormal basic strength is almost certainly related to the structure of the base rather than that of the ion. Similar considerations apply to 5-aminoquinoline.

The aminocinnolines also provide evidence of the lack of interaction between $N_{(1)}$ and $C_{(5)}$. The two adjacent ring-nitrogen atoms should lead to higher N–H bond-stretching force constants for all positions of substitution. However, if the 1 : 5-effect operates as in 5-aminoquinoline, 5-aminocinnoline should have the force constant characteristic of non-interacting systems. The value obtained (6·56 $\times$ 10^5 dyne cm.$^{-1}$) is almost identical with

[27] Calderbank and Le Fèvre, *J.*, 1951, 649.
[28] Daudel and Chalvet, *J. Chim. phys.*, 1949, **46**, 332; Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.

that for 5-aminoquinoline. 5-Aminoquinazoline should resemble 8-amino*iso*quinoline in the characteristics of the amino-group, and this is found to be so.

The effect of two ring-nitrogen atoms adjacent to the amino-group is shown in 2-aminoquinazoline. As is to be expected, the N–H force constant is very high and similar to that for 2-aminopyrimidine.

In view of previous results for 8-aminoquinoline and 1-aminoacridine it was expected

TABLE 3.

Compound	In CCl_4			In $CHCl_3$			In pyridine	
	ν_a	ν_s	k *	ν_a	ν_s	k *	ν_a	ν_s
3-Amino*iso*quinoline	3507	3407	6·62	3503	3405	6·61	—	—
4- ,, ...	3474	3393	6·53	3477	3397	6·54	—	—
5- ,, ...	3484	3401	6·56	3481	3399	6·55	—	—
6- ,, ...	3500	3407	6·61	3500	3410	6·61	—	—
7- ,, ...	3489	3402	6·58	3481	3401	6·56	—	—
8- ,, ...	3490	3407	6·59	3484	3405	6·57	3361	3230
2-Aminoquinazoline	3543	3431	6·73	3531	3421	6·69	—	—
4- ,, [b]	3537	3423	6·61	—	—	—	—	—
5- ,, ...	3489	3406	6·58	3489	3407	6·59	—	—
6- ,, ...	3495	3405	6·59	3495	3406	6·59	—	—
7- ,, ...	3506	3411	6·63	3504	3414	6·63	3349	3203
8- ,, ...	3502	3395	6·59	3497	3393	6·57	3457	3319
3-Aminocinnoline	3510	3405	6·62	3505	3403	6·61	—	—
4- ,, ...	Insol.	—	—	3505	3421	6·64	—	—
5- ,, ...	3481	3397	6·55	3481	3401	6·56	—	—
6- ,, ...	Insol.	—	—	3506	3413	6·63	—	—
7- ,, ...	3501	3410	6·62	3502	3410	6·62	3345	3211
8- ,, ...	3509	3399	6·61	3505	3398	6·60	3458	3316
2-Aminopyrimidine	3541	3431	6·68	—	—	—	—	—
4- ,, ...	3535	3423	6·64	—	—	—	—	—
5- ,, ...	3486	3401	6·52	—	—	—	—	—
5-Aminoquinoline	3477	3397	6·54	3479	3400	6·55	—	—

* N–H force constant (10^5 dyne cm.$^{-1}$). [b] Slightly sol. in cold; saturated solution at 50—60° used.

that intramolecular hydrogen bonding would occur in 8-amino-quinazoline and -cinnoline. As before,[5] it was found that the lowering of N–H frequencies in pyridine solution was very much less for these compounds than for other isomers, indicating the existence of hydrogen bonds which prevent bonding with the solvent. In other cases (*e.g.*, 1-aminoacridine, 8-aminoquinoline) such hydrogen bonding is associated with lowering of the pK_a value. The failure of 8-aminocinnoline to show such lowering clearly indicates $N_{(2)}$ as the basic centre. Lowering is observed with 8-aminoquinazoline and might be taken to indicate that $N_{(1)}$ is the basic centre, but the case is complicated as is discussed above.

MATERIALS

The aminocinnolines have been described elsewhere.[29]

The amino-*iso*quinolines and -quinazolines were known previously, so that frequently we merely describe purification procedures, but in certain cases modified preparations require comment.

3-Amino*iso*quinoline was recently synthesised by a somewhat elaborate route from 3-methyl*iso*quinoline.[30] 3-Chloro*iso*quinoline, obtained from 1 : 3-dichloro*iso*quinoline[31] (catalytic reduction gave only *iso*quinoline), has now been aminated. A similar sequence of reactions with 1 : 3-dibromo*iso*quinoline, obtained from homophthalimide, was not advantageous. 5-Nitro*iso*quinoline was best reduced to the amine with palladised charcoal in methanol. Although we improved the preparation of *m*-methoxy-ω-nitrostyrene we could not reduce it satisfactorily,[32] and resorted to the laborious but very efficient preparation of the amine and derived 1 : 2 : 3 : 4-tetrahydro-6-methoxy*iso*quinoline described by

[29] Osborn and Schofield, *J.*, 1955, 2100.
[30] Teague and Roe, *J. Amer. Chem. Soc.*, 1951, **73**, 688; Case, *J. Org. Chem.*, 1952, **17**, 471.
[31] Haworth and Robinson, *J.*, 1948, 777.
[32] Cardwell and McQuillin, *J.*, 1949, 708.

Helfer.[33] Robinson [34] dehydrogenated the tetrahydro-compound with Raney nickel in naphthalene: this we could not repeat, but found palladised charcoal a satisfactory catalyst. 6-Methoxy*iso*quinoline was converted into the amine by known methods.[34,35] Robinson [34] prepared 7-amino*iso*quinoline from the hydroxy-compound, and we merely report experimental details. As a possible alternative route 4-nitrohomophthalic acid was converted into 1 : 3-dihydroxy-7-nitro*iso*quinoline by the general method of Bergstrom and Wirth.[36] Chlorination gave 1 : 3-dichloro-7-nitro*iso*quinoline, but subsequent attempts to reproduce the reaction failed, possibly because the initial experiment was carried out with a very old specimen of phosphorus oxychloride. Lack of material precluded careful study of the reduction of the dichloro-compound. Previous preparations [34,37] of 8-amino*iso*quinoline were impracticable. Catalytic reduction of 5-chloro-8-nitro*iso*quinoline with palladised calcium carbonate in methanol, in the presence of sodium acetate, gave only a moderate yield of 8-amino*iso*quinoline, but excellent recovery was obtained when ammonium acetate replaced the sodium salt. Other reductions of 5-chloro- and 5-bromo-8-nitro*iso*quinoline are described below.

2-Chloroquinazoline was converted into 2-phenoxyquinazoline, which with fused ammonium acetate provided the corresponding amine. More convenient was Macbeth and Rodda's method [38] for details of which we are indebted to Dr. Rodda. Naff and Christensen [39] obtained 5-aminoquinazoline by catalytic reduction of 4-chloro-5-nitroquinazoline followed by dehydrogenation of the dihydro-compound (not isolated) with palladised charcoal; these workers found it necessary to shake the chloro-compound with Raney nickel in ethylene glycol monomethyl ether before carrying out reduction with palladised calcium carbonate, and were troubled by the instability of the dihydro-compound; we found that, provided pure 4-chloro-5-nitroquinazoline was used, preliminary treatment with Raney nickel was unnecessary and the dihydroquinazoline could be oxidised in the usual way with potassium ferricyanide. 6-, 7-, and 8-Aminoquinazoline were prepared by the methods of Elderfield *et al.*[25] and of Naff and Christensen [39] with the difference that the catalytic reductions were effected at atmospheric pressure with a 6% palladised-charcoal catalyst.

Attempts to prepare 6-aminophthalazine failed. Reduction of 1-chloro-7-methoxyphthalazine with red phosphorus and hydriodic acid gave 6-hydroxyphthalazine,[40] but under the conditions of the Bucherer reaction this gave only traces of diazotisable material.

6 : 7-Benzoquinazoline was described by Etienne and Legrand [41] who obtained it from its 4-chloro-derivative. From the same source Legrand [42] prepared 4-amino-6 : 7-benzoquinazoline. No experimental details of any of these reactions have been given, and these we supply below. With the aim of synthesising 4-methyl-6 : 7-benzoquinazoline by the method used by Elderfield and Serlin [43] in the quinazoline series, 4-chloro-6 : 7-benzoquinazoline was converted into diethyl 6 : 7-benzoquinazol-4-ylmalonate which with methanolic potassium hydroxide gave methyl 6 : 7-benzoquinazol-4-ylacetate. Hydrolysis of the latter provided only a trace of what appeared to be a hydrated form of the desired 4-methyl compound.

Quinoline and *iso*quinoline methochlorides were obtained by treating the aqueous solutions of the methiodides with silver chloride. Similarly, the products obtained by treating cinnoline and 4-methylcinnoline with methyl iodide were converted into chlorides. A similar attempt to prepare 4-methylquinazoline methochloride gave a pale orange glass. 3-Methylquinazolinium chloride was prepared *in situ* by dissolving the related hydroxide [20] in hydrochloric acid as required. We confirmed the identity of this compound with the

[33] Helfer, *Helv. Chim. Acta*, 1924, **7**, 945.
[34] Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1939, 1944.
[35] Manske and Kulka, *ibid.*, 1950, **72**, 4997.
[36] Bergstrom and Wirth, U.S.P., 2,351,391/1944.
[37] Andersag, *Med. Chem. Abhandl. a. med. chem.*, 1934, **2**, 377.
[38] Macbeth and Rodda, *Nature*, 1945, **156**, 207.
[39] Naff and Christensen, *J. Amer. Chem. Soc.*, 1951, **73**, 1372.
[40] Cf. Gabriel, *Ber.*, 1903, **36**, 3373.
[41] Etienne and Legrand, *Compt. rend.*, 1949, **229**, 220.
[42] Legrand, *ibid.*, 1950, **231**, 1318.
[43] Elderfield and Serlin, *J. Org. Chem.*, 1951, **16**, 1669.

unambiguously synthesised 3-methyl compound,[21] and observed that the m. p. of "3-methylquinazolinium picrate" was extremely sensitive to the presence of moisture (see above).

Experimental

After purification the compounds used in physical measurements were thoroughly dried *in vacuo* over phosphoric anhydride. 4-Amino*iso*quinoline gave cream nodules, m. p. 108—109·5°, from benzene–*cyclo*hexane. 6-Amino*iso*quinoline formed small cream crystals, m. p. 211—212°, from benzene. 4-Aminoquinazoline gave colourless needles, m. p. 271—272°, from ethanol. 6-Aminoquinazoline formed yellow rhombs, m. p. 213—214°, from benzene. 7-Aminoquinazoline, sublimed twice (160°/0·5 mm.) and crystallised from benzene, formed cream leaflets, m. p. 190—191°. Similar purification of 8-aminoquinazoline (sublimation at 120°/0·5 mm.) gave bright yellow prisms, m. p. 150—151°.

Catalytic Reduction of 1 : 3-*Dichloro*isoquinoline.—When the dichloro-compound (0·5 g.), methanol (25 c.c.), potassium hydroxide (0·4 g.), and Raney nickel (3 c.c.) were shaken with hydrogen, 2 equivs. of the latter were quickly absorbed. The filtered solution was acidified and freed from methanol. The ether extract of the basified residue gave, with ethereal picric acid, *iso*quinoline picrate, m. p. and mixed m. p. 225—226°. 1 : 3-Dibromo*iso*quinoline behaved similarly.

1 : 3-*Dibromo*isoquinoline.—Homophthalimide (5 g.) and phosphorus tribromide (50 c.c.) were refluxed for 5 hr. Removal of excess of phosphorus tribromide under reduced pressure, and treatment of the residue with alkali, gave colourless 1 : 3-*dibromoisoquinoline* (3·4 g.), m. p. 147—147·5° (Found : C, 38·85; H, 1·9. $C_9H_5NBr_2$ requires C, 37·8; H, 1·75%), from methanol.

3-*Bromo*isoquinoline.—The dibromo-compound (3 g.), reduced by Haworth and Robinson's method,[21] gave 3-bromo*iso*quinoline (1·75 g.), m. p. 63—64° (from aqueous methanol) (Found : C, 52·5; H, 3·0. Calc. for C_9H_6NBr : C, 51·9; H, 2·9%).

3-*Amino*isoquinoline.—3-Chloro*iso*quinoline (8·8 g.), aqueous ammonia (*d* 0·88; 100 c.c.), and copper sulphate (1 g.) were heated at 140° for 30 hr. in an autoclave. The cold mixture was strongly basified and extracted with chloroform. The extract provided 3-amino*iso*quinoline (5·3 g.), m. p. 174—177°. Several recrystallisations from benzene gave bright yellow plates, m. p. 176—177° (Found : C, 74·9; H, 5·6; N, 19·6. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6; N, 19·4%). 3-Bromo*iso*quinoline was aminated similarly.

5-*Amino*isoquinoline.—5-Nitro*iso*quinoline (20 g.), shaken in methanol (500 c.c.) with palladised charcoal (2 g., 5%) and hydrogen, was reduced in 2 hr. The residue from filtration and evaporation, when dissolved in chloroform and poured into light petroleum (b. p. 40—60°), gave the amine (93%), m. p. 128—129°. This was purified by repeated crystallisation from benzene–*cyclo*hexane, and obtained as straw-coloured plates which changed to blades, m. p. 129·5—130·5°, in the presence of the solvent.

m-*Methoxy-ω-nitrostyrene.*—*m*-Methoxybenzaldehyde (35·5 g.), nitromethane (18 g.), acetic acid (125 c.c.), and ammonium acetate (12·5 g.) were refluxed gently for 2 hr. The solution was poured into iced water and the precipitate was recrystallised from benzene, giving yellow plates (27 g.), m. p. 91—92°.

6-*Hydroxy*isoquinoline.—1 : 2 : 3 : 4-Tetrahydro-6-methoxy*iso*quinoline (2·42 g.) (Helfer [33]) and palladised charcoal (0·8 g.; 30% Pd) were heated at 180—190° for ½ hr. in a stream of nitrogen. Treatment with ether, filtration and removal of the solvent gave a pale brown oil (2·1 g.) which was treated in acetone (10 c.c.) with picric acid (3 g.) in the same solvent. The bright yellow picrate (2·9 g.) was decomposed with aqueous lithium hydroxide, and the product was recovered by ether-extraction. The resulting pale yellow oil (1·03 g.) was refluxed for 2 hr. with concentrated hydrobromic acid (25 c.c.), excess of which was then removed under reduced pressure. The residue in water (10 c.c.) was treated with sodium carbonate solution, and the product [0·85 g.; m. p. 220° (decomp.)] was collected and washed.

1 : 3-*Dihydroxy*-7-*nitro*isoquinoline.—4-Nitrohomophthalic acid (56 g.) and *o*-dichlorobenzene (8 parts) were treated as described by Bergstrom and Wirth.[34] During the reaction a red solid separated which was collected and washed with dichlorobenzene, hot water, alcohol, and ether. The deep red powder (52 g.), m. p. *ca.* 291° (decomp.), could not be purified by crystallisation or sublimation. It dissolved in alkali, forming a carmine-red solution. Acidification afforded a brownish-yellow precipitate which became brown in air and deep red in the presence of ammonia.

1 : 3-*Dichloro*-7-*nitro*isoquinoline.—The above (2 g.) and phosphorus oxychloride (20 c.c.) were heated for 4 hr. on the steam-bath. Decomposition with ice and basification (pH 10) gave a khaki-coloured solid which formed greenish-yellow crystals (1·18 g.), m. p. 179—182°, from

acetic acid. Further crystallisation gave the *dichloro-compound*, m. p. 185° (decomp.) (Found: C, 45·3; H, 1·7. $C_9H_4O_2N_2Cl_2$ requires C, 44·5; H, 1·7%).

7-Aminoisoquinoline.—7-Hydroxy*iso*quinoline (1·25 g.), saturated ammonium hydrogen sulphite solution [4 c.c.; prepared from aqueous ammonia (*d* 0·88) and sulphur dioxide], and aqueous ammonia (20 c.c.; *d* 0·88) were heated at 140—150° for 16 hr. The product was washed with 2N-sodium hydroxide and water, yielding a fawn powder (1·1 g.), m. p. 204°. Sublimation (150°/0·3 mm.) and two crystallisations from benzene gave pale yellow needles, m. p. 203—205°.

5-Bromoisoquinoline.—5-Amino*iso*quinoline (4·8 g.) in concentrated hydrobromic acid (12 c.c.) and water (13 c.c.) was diazotised at 0° with sodium nitrite (2·3 g.) in water (15 c.c.). The diazonium solution was added slowly to a stirred solution of cuprous bromide (5·8 g.) in hydrobromic acid (48 c.c.) at 75°. After 24 hr. at room temperature the solution was basified and steam-distilled, giving 5-bromo*iso*quinoline (5·1 g.), m. p. 82—84° after recrystallisation from light petroleum (b. p. 40—60°).

5-Bromo-8-nitroisoquinoline.—Potassium nitrate (2·4 g.) in concentrated sulphuric acid (20 c.c.) was added during 5 min. to 5-bromo*iso*quinoline (4·15 g.) in the same acid (24 c.c.) stirred at 20°. After 1 hr. at room temperature the solution was poured on ice and basified with aqueous ammonia. Crystallisation from methanol of the washed and dried precipitate gave 5-bromo-8-nitro*iso*quinoline (5·05 g.), m. p. 139—141°.

8-Aminoisoquinoline.—Palladised calcium carbonate (2 g.; 6% Pd) and absolute methanol were shaken for a short time with hydrogen. Pure 5-chloro-8-nitro*iso*quinoline (2 g.) and ammonium acetate (12 g.) were then added and shaking was continued. In 1 hr. hydrogen (10% in excess of the theor.) was absorbed. The filtered solution was acidified with concentrated hydrochloric acid and methanol was removed under reduced pressure on the steam-bath. The solution of the orange-yellow residue in water was basified with saturated aqueous sodium carbonate and extracted with chloroform. The dried extract provided felted needles (1·36 g.) which from ethyl acetate formed very pale yellow needles (1·02 g.), m. p. 168—172°. Very pale fawn prisms of pure 8-amino*iso*quinoline, m. p. 171—172° (Found: C, 75·2; H, 5·5. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6%), were obtained by further crystallisation from ethyl acetate. Andersag [37] gave m. p. 174°. From a similar reduction in which sodium acetate was used a lower yield of impure amine was obtained. Reduction with palladised charcoal in methanol in the presence of sodium acetate merely produced 8-amino-5-chloro*iso*quinoline in high yield. The chlorine atom in this compound could not be removed by hydrogenation in presence of Raney nickel in alkaline solution. When 5-bromo-8-nitro*iso*quinoline in methanol was hydrogenated in presence of palladised calcium carbonate the solution became red and then green, and a green precipitate, probably of the intermediate hydroxylamine, was formed. A similar experiment in the presence of potassium hydroxide produced a small yield of 8-amino*iso*quinoline after elaborate purification.

2-Aminoquinazoline.—2-Chloroquinazoline (0·5 g.) was added slowly to a solution of potassium hydroxide (0·4 g.) in phenol (5 g.) on the steam-bath. The mixture was heated for 3 hr. at 70°. Basification and filtration gave a light-brown solid (0·58 g.) which from light petroleum (b. p. 60—80°) formed colourless needles of 2-phenoxyquinazoline, m. p. 124—126°. This (0·5 g.) was heated with ammonium acetate (5 g.) at 170—180° for 2 hr. After cooling, water and 2N-sodium hydroxide were added and the product (0·35 g.) was crystallised from ethanol. It formed yellow crystals, m. p. 200°.

4-Hydroxy-5-nitroquinazoline.—6-Nitroanthranilic acid (14·84 g.) and formamide (29·4 c.c.) were heated at 155—160° (bath-temp.) for 4½ hr. The product was triturated with a little water and crystallised from the same solvent (charcoal), giving matted needles (12·2 g.), m. p. 252—256°.

4-Chloro-5-nitroquinazoline.—The hydroxy-compound (7 g.) was chlorinated as described by Naff and Christensen.[38] Excess of phosphorus oxychloride was removed under reduced pressure and the residue, after treatment with ice and excess of 4N-sodium hydroxide, was extracted rapidly with ether. The solid (5·17 g.) so recovered was sublimed (140°/0·5 mm.), giving pure 4-chloro-5-nitroquinazoline as a cream solid, m. p. 142°.

5-Aminoquinazoline.—The chloro-compound (1 g., resublimed), dry ethylene glycol monomethyl ether (150 c.c.) and palladised calcium carbonate (0·5 g.; 6% Pd) were shaken with hydrogen. Reduction was complete in ½ hr., and the solution was filtered and evaporated under reduced pressure with gentle warming. The residue was oxidised by the method of Elderfield *et al.*,[35] and the brown gum isolated by chloroform-extraction of the oxidation solution was chromatographed on alumina, being eluted successively with benzene, benzene–ether, and ether. The yellow band removed by the last solvent arose from an orange-yellow solid

(0·265 g.) which formed long orange needles, m. p. 195—197°, from benzene. For physical measurements it was recrystallised several times and sublimed (160°/1 mm.), giving chrome-yellow needles, m. p. 195—196·5°.

1-*Chloro*-7-*methoxyphthalazine* (cf. Vaughan and Bird [44]).—The hydroxy-compound (8·8 g.) and phosphorus oxychloride (40 c.c.) were heated on the steam-bath until dissolution occurred, and then refluxed for ½ hr. more. The cooled liquid was poured on ice and basified. The precipitate [7·4 g.; m. p. 142° (decomp.)] was not further purified.

6-*Hydroxyphthalazine*.—The above compound (0·5 g.), red phosphorus (0·2 g.), and hydriodic acid (b. p. 127°; 5 c.c.) were refluxed for 1 hr. The mixture was diluted with water (5 c.c.) and after filtration evaporated to dryness under reduced pressure. The solution of the dark brown solid residue in warm water (5 c.c.) was adjusted to pH 7 with aqueous ammonia. The resulting precipitate gave the product (0·3 g.), m. p. *ca.* 300° (decomp.) (in a bath preheated to 290°), when crystallised from water. Recrystallisation gave 6-*hydroxyphthalazine* as yellow crystals of unchanged m. p. (Found: C, 60·1; H, 4·5; N, 17·3. $C_8H_6ON_2,\frac{1}{2}H_2O$ requires C, 60·8; H, 4·7; N, 17·7%). This compound was readily soluble in alkali and gave a faint red-brown colour with ferric chloride.

1-Chloro-7-methoxyphthalazine, refluxed with hydrobromic acid, gave 4 : 6-*dihydroxyphthalazine*, m. p. 310° (decomp.) (Found: C, 56·1; H, 4·0. $C_8H_6O_2N_2$ requires C, 56·1; H, 4·1%), which separated as a cream solid from water. The m. p. was strongly depressed on admixture with 6-hydroxyphthalazine.

6 : 7-*Benzoquinazoline*.—By Niemetowsky's method [45] 3-amino-2-naphthoic acid (10 g.) gave 4-hydroxy-6 : 7-benzoquinazoline (8·5 g.), which separated from water as a pale yellow solid, m. p. 278°. This compound (1·3 g.) and phosphorus oxychloride (20 c.c.) were refluxed for 2 hr. The product, a bright yellow solid (0·98 g.), m. p. 173°, was isolated in the usual way. Sublimation (160°/0·1 mm.) gave the almost pure product, m. p. 176—178°.

Reduction of the chloro-compound (0·44 g.) in ethylene glycol monomethyl ether (50 c.c.) with palladised calcium carbonate (0·5 g.; 8% Pd) and hydrogen was complete in 1½ hr. The catalyst was removed and the solution was evaporated under reduced pressure, with gentle warming. The residue was boiled with water, the solution was filtered, and oxidation with potassium ferricyanide (1·4 g.) was effected in the usual way. From the oxidation solution chloroform removed a dark brown solid which gave bright yellow crystals (0·19 g.; m. p. 150—160°) on sublimation (110°/1 mm.). From *cyclo*hexane it gave bright yellow crystals, m. p. 163—165°. Etienne and Legrand [41] gave m. p. 160°.

4-*Amino*-6 : 7-*benzoquinazoline*.—The chloro-compound (0·23 g.) and saturated anhydrous methanolic ammonia (25 c.c.) were refluxed for 2 hr. The precipitate, combined with material obtained by evaporating the solvent, was washed with warm water and dried, giving a yellow solid (0·18 g.), m. p. *ca.* 300° (decomp.). Three sublimations (130°/0·1 mm.) and recrystallisation from ethanol gave the amine, m. p. *ca.* 365° (decomp.) (in a bath preheated to 360°). Legrand [42] gave m. p. 363°.

Diethyl 6 : 7-*Benzoquinazol*-4-*ylmalonate*.—4-Chloro-6 : 7-benzoquinazoline (2·1 g.) in warm benzene (100 c.c.) was added to a suspension of sodiomalonic ester (2 equivs.) in benzene (100 c.c.). After being refluxed for 3 hr. and left overnight the deep orange mixture was poured into water. Evaporation of the dried (Na_2SO_4) organic layer and crystallisation of the residue from ethanol gave *diethyl* 6 : 7-*benzoquinazol*-4-*ylmalonate* (2·29 g.) as bright yellow needles, m. p. 172—175° (Found: C, 68·1; H, 5·5. $C_{19}H_{18}O_4N_2$ requires C, 67·4; H, 5·4%).

Methyl 6 : 7-*Benzoquinazol*-4-*ylacetate*.—The above product (1·5 g.), potassium hydroxide (0·6 g.), and methanol (60 c.c.) were refluxed for 3 hr. The orange-red solution quickly became yellow, and, on cooling, deposited yellow needles (0·58 g.). Recrystallisation from methanol gave ginger-yellow needles of the *ester*, m. p. 207—209° (forming a red melt) (Found: C, 71·6; H, 4·9; N, 11·5. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%). No pure product was isolated from the reaction mother-liquor.

Hydrolysis of this ester with boiling aqueous sodium hydroxide gave only traces of a steam-volatile, benzene-soluble compound, which formed pale yellow crystals, m. p. 124—126° after repeated crystallisation from light petroleum (b. p. 40—60°), and appeared to be hydrated 4-*methyl*-6 : 7-*benzoquinazoline* (Found: C, 70·1; H, 6·0. $C_{13}H_{10}N_2,1{\cdot}5H_2O$ requires C, 70·6; H, 5·9%).

iso*Quinoline Methochloride*.—*iso*Quinoline (5 g.), methyl iodide (10 c.c.), and methanol were

[44] Vaughan and Bird, *J. Amer. Chem. Soc.*, 1946, **68**, 1314.
[45] Niemetowsky, *J. praht. Chem.*, 1895, **51**, 565.

refluxed for 2 hr. Removal of the solvent and crystallisation from ethanol gave lemon-yellow needles, m. p. 160—161·5°, which were shaken with water (50 c.c.) and excess of freshly precipitated silver chloride for 12 hr. Filtration and evaporation at reduced pressure gave glistening needles which were crystallised from ethanol–ether and collected on a sintered-glass plate in an apparatus from which moisture was excluded.

In the same way quinoline methochloride was obtained as thick deliquescent needles.

Cinnoline Methochloride.—Cinnoline methiodide was prepared from cinnoline in the usual way and freed from unchanged starting material by extraction (Soxhlet) with light petroleum (b. p. 40—60°). The lilac-coloured solution obtained after conversion into the *methochloride*, when evaporated *in vacuo* at 20° gave a lilac-coloured solid which after three crystallisations (charcoal) from dry ethanol–ether gave very pale yellow plates (Found: C, 56·9; H, 5·3; N, 18·6. $C_9H_9N_2Cl,\frac{1}{2}H_2O$ requires C, 57·1; H, 5·6; N, 18·7%). These were very deliquescent, changing in air to a deep-blue liquid. They were manipulated in a filtration apparatus protected from moisture, and stored without difficulty over phosphoric anhydride in a vacuum-desiccator.

4-*Methylcinnoline methochloride* obtained in the same way and with the same precautions formed very pale blue-green needles (Found: C, 56·8; H, 6·0; N, 16·9. $C_{10}H_{11}N_2Cl,H_2O$ requires C, 56·5; H, 6·1; N, 16·7%), which were very deliquescent and formed a dark green liquid when exposed to the atmosphere.

Physical Measurements.—The ultraviolet measurements were made in the usual way, with a Unicam S.P. 500 instrument. The buffer solutions used (which, when possible, had a constant strength of 0·01M) were: glycine–hydrochloric acid (pH 2·5—3·7), sodium acetate–acetic acid (pH 4·0—5·6), potassium dihydrogen phosphate–sodium borate (pH 7·0—9·2), sodium borate (pH 9·21). The pH values of all solutions above pH 2 were measured by means of a meter. For values below pH 2·5 standard solutions of hydrochloric acid were used.

The deliquescent methochlorides were made up as approximately 0·01M-solutions in water, and concentrations were then determined by titrating the chloride ion with silver nitrate. For both spectroscopic and pK_a determinations cinnoline and *iso*quinoline were purified by repeated vacuum-distillation, specimens being collected finally in small glass bulbs of known weight which were immediately sealed and subsequently broken under water when solutions were being prepared.

Ionisation constants were determined by potentiometric titrations of aqueous solutions with hydrochloric acid in a thermostat at 20° ± 0·05°. pH measurements were made with a Cambridge instrument in conjunction with a glass electrode. The latter was standardised by means of 0·05M-sodium borate (pH 9·23) and 0·05M-potassium hydrogen phthalate (pH 4·00) [British Standard pH Scale, **1647** (1950)]. pK_a values were calculated from the titration curves at 30, 40, 50, 60, and 70% neutralisation by using the equation $pK_a = pH + \log x/(100 - x)$ (x = % neutralisation), or with weaker bases $pK_a = pH + \log([HCl] - [H^+])/([B^+] - [HCl] + [H^+])$.[46] pK_a values for phenanthridine, 6-aminophenanthridine, and 6 : 7-benzoquinazoline were determined spectrophotometrically. Ultraviolet extinction curves were determined for the compounds in a number of buffer solutions, and calculations made by the method of Irvin and Irvin.[47] In the case of 6 : 7-benzoquinazoline true isosbestic points were not obtained (probably because of intense fluorescence). Calculations at the longest wavelength gave $pK_a \sim 5·2$.

Infrared measurements were made in dried and distilled solvents, a Perkin–Elmer instrument with a lithium fluoride prism being used.

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[*Received, April 25th*, 1956.]

[46] Britton, "Hydrogen Ions," Chapman and Hall, London, 1942.
[47] Irvin and Irvin, *J. Amer. Chem. Soc.*, 1947, **69**, 1091.

811. *Cinnolines. Part XXXV.* Studies of the Chloro- and Hydroxy-cinnolines.*

By A. R. Osborn and K. Schofield.

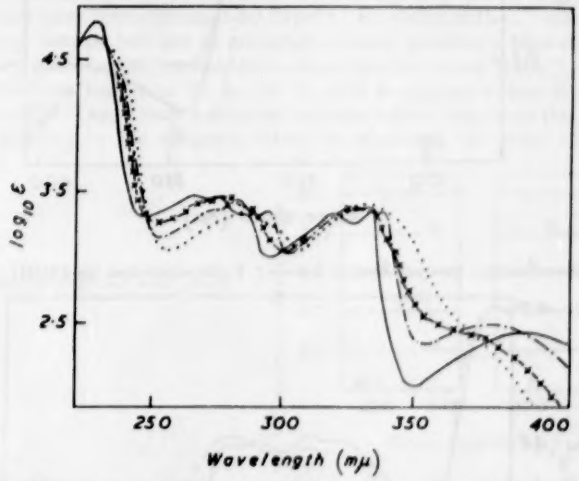
6-, 7-, and 8-Chlorocinnoline are described. The effect of chloro-substituents upon the cinnoline ultraviolet absorption spectrum, particularly the n–π^* band is discussed.

The ionisation constants of the hydroxycinnolines are reported and evidence for the importance of zwitterionic forms is discussed.

In studying the ultraviolet absorption spectra and basic strengths of the aminocinnolines (preceding paper) we found it desirable to examine other derivatives of this system, notably the chloro- and hydroxy-compounds.

(a) *Chlorocinnolines.*—In Figs. 1, 2, and 3 we give the ultraviolet extinction curves for 3-, 4-, 6-, 7-, and 8-chlorocinnoline in *cyclo*hexane and (except for the reactive 4-isomer)

Fig. 1. *3-Chlorocinnoline* (*in* cyclo*hexane*) — . — . —; *3-chlorocinnoline* (*in* EtOH) . . . . .; *7-chlorocinnoline* (*in* cyclo*hexane*) ———; *7-chlorocinnoline* (*in* EtOH) — × — × —.



in ethanol. Generally the band systems corresponding to those with $\lambda < 350$ mμ in the cinnoline spectrum [1] show bathochromic displacements as would be expected of bands produced by π–π^* transitions.

Tombácz [2] correlated the bands at about 300 mμ in the quinoline and *iso*quinoline spectra, and the band at 310 mμ in that of quinoxaline, with the naphthalene band at 308 mμ. All these bands were considered to arise from transitions polarised along the major axis of the molecules. Similarly the bands at 260—270 mμ for quinoline, *iso*quinoline, and quinoxaline, and at 275 mμ for naphthalene were related to transitions polarised along the minor axis. The π–π^* bands of the cinnoline absorption spectrum are very similar to those of *iso*quinoline, and the 322—317 and 308 mμ peaks in the former case may be related to those at about 300 and 260—270 mμ in the latter case.

The qualitative effects upon the positions of these bands of the substituents in the chlorocinnolines are only roughly in agreement with these assignments. Thus, the first long-wavelength π–π^* band suffers a bathochromic shift of 16, 11, 8, and 4 mμ in the

* Part XXXIV, *J.*, 1955, 2100.

[1] Hearn, Morton, and Simpson, *J.*, 1951, 3318.

[2] Tombácz, *Magyar Kém. Folyóirat*, 1950, **56**, 175.

3-, 7-, 8-, and 4-chloro-compounds respectively. The biggest shifts are produced by substituents at $C_{(5)}$ and $C_{(7)}$, as would be expected if the band is associated with a transition polarised along the major axis of the cinnoline nucleus. The effect of a 6-chloro-substituent in producing a very small hypsochromic shift is, in these terms, anomalous. With the medium-wavelength band, the effect of the substituent in 8-chlorocinnoline (bathochromic

FIG. 2. *4-Chlorocinnoline* (*in* cyclo*hexane*) ———; *6-chlorocinnoline* (*in* cyclo*hexane*) . . . . .; *6-chlorocinnoline* (*in* EtOH) – – – – –.

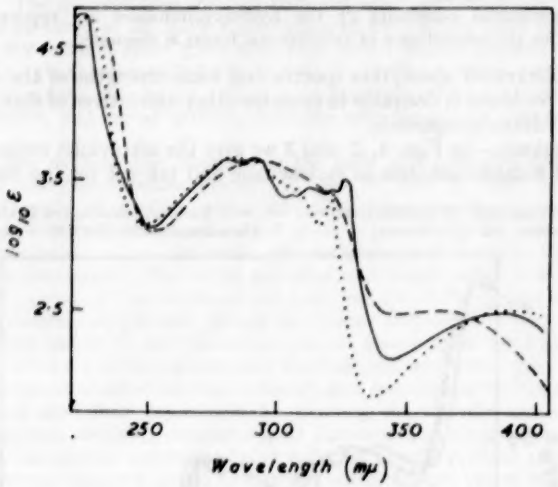
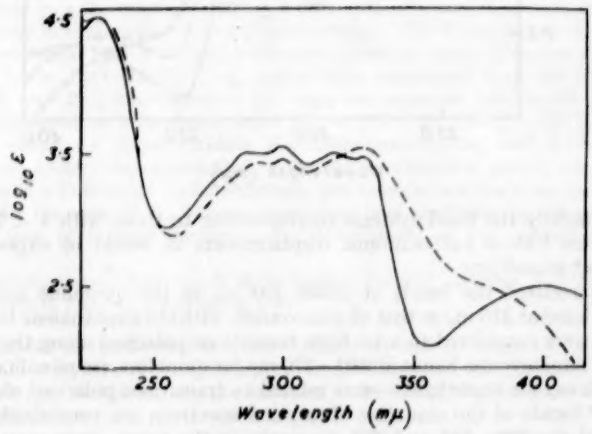


FIG. 3. *8-Chlorocinnoline* (*in* cyclo*hexane*) ———; *8-chlorocinnoline* (*in* EtOH) – – – – –.



shift of 12 mμ) is to be expected if the band is connected with a transition polarised along the minor axis. However, the cases of 3-, 4-, 6-, and 7-chlorocinnoline (bathochromic shifts of 8, 6, 4, and 0 mμ respectively) are not simply related to such a picture. The strong interaction of the two nitrogen atoms presumably disturbs the situation. Examination of the extinction curves shows that those of the 3- and the 7-isomer are very similar, as are those of the 4- and the 6-compound. The curve for 8-chlorocinnoline is slightly different from those of the latter pair.

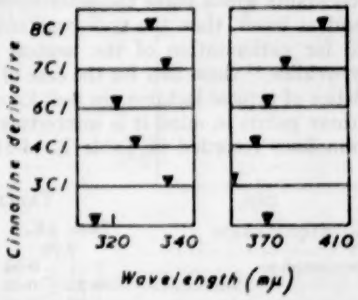
With regard to the intensities of the long-wavelength bands of the π–π^* spectra, application of the spectroscopic moments developed by Platt [3] would indicate an increase in the intensity ($\Delta\varepsilon$ +492) with 3- and 7-chlorocinnoline, and a decrease ($\Delta\varepsilon$ −192) with 4-, 5-, 6-, and 8-chlorocinnoline as compared with cinnoline. The observed changes in intensity ($\Delta\varepsilon$ +58, +871, +9, +211, and +871 for 3-, 4-, 6-, 7-, and 8-chlorocinnoline respectively) differ greatly from those predicted, but it is noteworthy that the 3-, 6-, and 7-isomers form a group, as do the 4- and 8-compounds. In the former group the resultant dipole falls more nearly along the short axis of the molecule, and in the latter group along the long axis.

The extinction curve of cinnoline in *cyclo*hexane [1] differs from those of related monoazanaphthalenes such as *iso*quinoline [4] most markedly in showing an additional low-intensity band (log $\varepsilon_{max.}$ 2·42) at 390 mμ. Hearn, Morton, and Simpson [1] remarked that this band " might well owe its origin to the presence of the –N=N– group in the molecule," and later authors [5,6] have identified it as arising from an n–π^* transition. Our observations on cinnoline support this assignment. Whilst the three main absorption bands (π–π^*) move slightly towards the red with change of solvent from *cyclo*hexane to water, that due to the n–π^* transition disappears (preceding paper) as would be expected.[7]

In studying the spectra of the diazines, Halverson and Hirt [8] observed that the introduction of chloro-substituents produced blue-shifts in the n–π^* band, and their results for the chloropyrazines have been discussed by Orgel.[9] He deduced that " substituents which can act as electron donors, but not as acceptors, should produce a blue-shift of the n–π^* spectra, since they stabilise the ground state more than the upper state."

With the extinction curves of 3-, 4-, 6-, 7-, and 8-chlorocinnoline it should first be noticed that again the change from non-polar to polar solvent produces the expected effect upon the n–π^* bands. In the diagram below we represent the effect of the change in

$\lambda_{max.}$ (mμ) *for* n–π^* *and* π–π^* *bands.*



position of the substituent upon the position of the n–π^* band and the longest-wavelength π–π^* band. In the cinnoline series the shifts in one band do not mirror those in the other as they do in the pyrazine series.[8] The n–π^* band undergoes a blue-shift with 3- and 4-chlorocinnoline, is unchanged with 6-chlorocinnoline, and shows a red-shift in 7- and 8-chlorocinnoline.

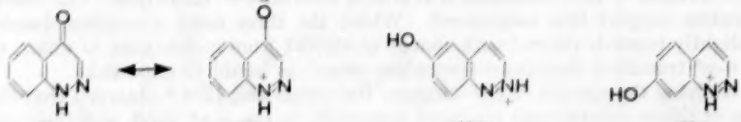
Clearly, in the bicyclic system the effect of the chloro-substituent upon the n–π^* band varies according to the position of the substituent. Qualitatively, this situation might be accounted for by recognising the dual character ($-I$, $+T$) of the chloro-substituent. The blue-shift caused by the 3- and 4-chloro-substituent could be caused by the strong $-I$ effect acting upon the $\sigma(n)$-electrons of the nitrogen atoms and increasing the strength of their binding. This influence will be in competition with the $+T$ effect of the substituent,

[3] Platt, *J. Chem. Phys.*, 1951, **19**, 263.
[4] Friedel and Orchin, " Ultra-violet Spectra of Aromatic Compounds," Wiley and Sons, New York, 1951, No. 271.
[5] Mason, " Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," *Chem. Soc. Special Publ.* No. 3, 1955, p. 139.
[6] Badger and Walker, *J.*, 1956, 122.
[7] Kasha, *Discuss. Faraday Soc.*, 1950, **9**, 14.
[8] Halverson and Hirt, *J. Chem. Phys.*, 1951, **19**, 711.
[9] Orgel, *J.*, 1955, 121.

which by extending the conjugated system will lower the energy of the excited state. At some point this second effect will predominate over the first and produce a red-shift. This apparently happens in 7- and 8-chlorocinnoline, whilst a balance is attained in 6-chlorocinnoline.

This sort of situation does not appear to have been observed before, but will probably arise in other benzodiazines.

(b) *Hydroxycinnolines.*—Discussion of the dissociation constants of hydroxyl derivatives of heteroaromatic systems in terms of the electronic character of the hydroxyl group ($-I$, $+T$) is complicated by the possibilities of lactam–lactim tautomerism and zwitterion formation. With α- and γ-" hydroxy "-compounds these two terms are synonymous and in these cases the importance of tautomerism has long been recognised. In all such cases examined [10] the equilibrium greatly favours the lactam form (*e.g.*, I ⟷ II). In some



(I) (II) (III) (IV)

cases it is possible to write zwitterionic structures for monohydroxy-compounds which are not stabilised by resonance, and the work of Metzler and Snell [11] on 3-hydroxypyridine shows that zwitterion formation does not depend on such stabilisation. With the *Bz*-hydroxycinnolines zwitterions could be stabilised to some extent by resonance in every case. Both lactam–lactim tautomerism and zwitterion formation lead to apparent dissociation constants which make the heterocyclic hydroxy-compounds appear weaker, both as acids and as bases, than the true constants for the simple ionisation of the hydroxyl group and for cationisation of the neutral molecule would indicate. The figures for 3-hydroxypyridine [11] show this for the case of a zwitterion, and the weak basic and acidic characteristics of typical lactams are well known.

With these points in mind it is interesting to consider the observed pK_a values of the hydroxycinnolines recorded in Table 1. 4-Hydroxycinnoline is firmly established as a

TABLE 1.

	Basic pK_a *	Molar concn.	Acidic pK_a *	Molar concn.
Cinnoline	2·29	—	—	—
3-Hydroxycinnoline	0·21 ± 0·04 ‡	0·0001	8·61 ± 0·02	0·002
4- ,,	−0·35 ± 0·05 ‡	—	9·27	—
5- ,,	1·92 ± 0·06	0·002	7·40 ± 0·02	0·001
6- ,,	3·65 ± 0·01	,,	7·52 ± 0·01	0·002
7- ,,	3·31 ± 0·02	,,	7·56 ± 0·02	,,
8- ,, †	2·71 ± 0·00 ¶	—	8·17	,,

* In water at 20°.
† See refs. 12 and 15 for other determinations.
‡ Personal communication from Professor A. Albert.
¶ Spectroscopic determination. Titration (0·002M) gave 2·56 ± 0·06.

compound in which the lactam structure (I ⟷ II) is of predominating importance, and the available ionisation constants [12] enable the amide : enol ratio to be calculated [13] if the reasonable assumption be made that the tautomerism involves $N_{(1)}$ [as in (I)]. The ratio is about 3600 : 1, compared with 24,000 : 1 for 4-hydroxyquinoline.[13] Although the evidence is not complete it is most probable that 3-hydroxycinnoline also exists mainly in the lactam form.[14] The ionisation constants suggest that the amide : enol ratio is lower than with 4-hydroxycinnoline.

[10] For bibliography see Albert in ref. 5, p. 130.
[11] Metzler and Snell, *J. Amer. Chem. Soc.*, 1955, **77**, 2431.
[12] Albert and Hampton, *J.*, 1954, 505.
[13] Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.
[14] Alford and Schofield, *J.*, 1953, 1811.

The acidic pK_a values show that, as would be expected, the *Bz*-hydroxycinnolines are stronger acids than phenol (pK_a 9·98) and the naphthols. The order of acid strengths ($5 > 6 > 7 > 8$) is not that to be expected from a simple consideration of the resonance stabilisation of the different anions. This is not surprising, for zwitterion formation probably occurs to a different degree in each case (see below) and the observed pK_a values are not the true constants for ionisation of the hydroxyl groups.

If the case of 5-hydroxycinnoline is disregarded, it will be seen that the order of basicities of the *Bz*-hydroxycinnolines is $6 > 7 > 8$ (ΔpK_a values being 1·36, 1·02, and 0·42). This is the order found for the aminocinnolines, the corresponding ΔpK_a values being 2·75, 2·56, and 1·39. The amino-group, because of its greater $+T$ effect, should be more base-strengthening. As with the amines, the problem arises with the hydroxy-compounds of deciding which nitrogen atom is the basic centre in each case (the unlikely possibility that the oxygen atom accepts the proton is eliminated by the cationic ultraviolet absorption spectra). In this connection the relatively large ΔpK_a values found for 6- and 7-hydroxycinnoline indicate that, as in the related amines, the basic centres are here $N_{(2)}$ and $N_{(1)}$ respectively, giving the resonance-stabilised cations (III) and (IV).

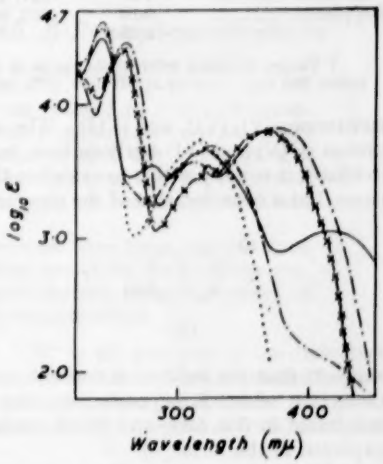


FIG. 4. *6-Hydroxycinnoline* (pH 5·43) ———; *6-hydroxycinnoline* (*in* EtOH) — · — · —; *6-hydroxycinnoline anion* (pH 10·0) – – – – –; *6-hydroxycinnoline cation* (0·1N-HCl) — × — × —; *6-methoxycinnoline* (pH 7) . . . . .

The case of 8-hydroxycinnoline is not so clear-cut. Previously [15] it was tentatively represented as having its basic centre at $N_{(1)}$, but consideration of 8-aminocinnoline (preceding paper) suggests that in 8-hydroxycinnoline $N_{(2)}$ might be the main site of cationisation. However, the small value of ΔpK_a in this case, and the lack of information regarding the possible steric influence of the hydroxyl group, makes a choice impossible. Irving and Rossotti [16] suggested that the greater basic strength of 8-hydroxy-4-methylcinnoline (pK_a 3·28) than of 8-hydroxycinnoline pointed to $N_{(1)}$ as the more basic nitrogen atom in 8-hydroxy-4-methylcinnoline. This assignment is rendered uncertain by the factors just mentioned and lack of knowledge of the basic strength of 4-methylcinnoline.

The ultraviolet extinction curves of 6-, 7-, and 8-hydroxycinnoline in roughly "neutral" solution (Fig. 4 and Table 2) resemble fairly closely the curves of the related methoxy-compounds except that they show additional maxima above 400 mμ ($\lambda_{max.}$ 414, 449, and 452, $\log_{10}\varepsilon$ 3·03, 2·47, and 2·55 for the 6-, 7-, and 8-isomers respectively). With 6-hydroxycinnoline another maximum ($\log_{10}\varepsilon$ 3·54) also appears at 280 mμ. In each case the relatively small separations of the basic and acidic ionisation constants made it possible that these additional maxima arose from the presence in "neutral" solutions of small concentration of anions and cations. That this is not so is shown clearly from the spectra of the hydroxy-compounds in media sufficiently alkaline or acidic to ensure almost complete conversion

[15] Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009.
[16] Irving and Rossotti, *J.*, 1954, 2910.

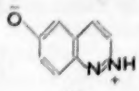
into the anion and cation respectively, and from the suppression of the additional maxima in alcohol solution. Clearly the subsidiary maxima must be ascribed to the presence in neutral solution not only of the uncharged molecule, but also of small concentrations of

TABLE 2. *Ultraviolet absorption spectroscopy of the hydroxycinnolines.*[a]

Cinnoline deriv.	Solvent or pH	$\lambda_{max.}$ (mμ)	$\log_{10} \varepsilon_{max.}$
5-Hydroxy	−0·25	257, 310, *328*, 410	4·47, 3·16, *3·05*, 3·28
	4·52	245, *300*, 357	4·53, *3·06*, 3·39
	11·0	234, 262, 338, *385*, *425*	4·23, 4·42, 3·48, *3·19*, 3·11
5-Methoxy	7·0	245, *305*, 353	4·53, *3·15*, 3·44
6-Hydroxy	0·1N-HCl	255, *310*, 324, 367	4·42, *3·40*, 3·53, 3·80
	5·43	240, 280, *310*, 320, 414	4·50, 3·54, *3·60*, 3·66, 3·03
	10·0	259, 311, 376	4·45, 3·57, 3·82
	EtOH	240, *259*, *308*, 325, *340*, *423*	4·61, *3·41*, *3·61*, 3·68, *3·59*, *2·04*
6-Methoxy	7·0	240, 316	4·56, 3·72
7-Hydroxy	0·1N-HCl	250, 307, *325*, 388	4·55, 3·53, *2·93*, 3·44
	5·43	236, 267, 358, 449	4·58, 3·66, 3·47, 2·26
	10·0	253, 286, 402, *428*	4·62, 3·82, 3·54, 3·39
	EtOH	237, *264*, *284*, *296*, *306*, 358	4·63, *4·00*, *3·68*, *3·43*, *3·07*, 3·59
7-Methoxy	7·0	237, 269, 346	4·66, 3·46, 3·50
8-Hydroxy[b]	0·10	252, 306, *322*, 430	4·46, 3·16, *2·95*, 3·39
	5·25[c]	296, 360, 452	3·11, 3·36, 2·55

[a] Values in italics refer to shoulders or inflexions. [b] Cf. ref. 16. [c] This curve was not continued below 260 mμ. Curves at pH 0·10, 5·25, and 2·01 gave an isosbestic point (λ 388 mμ, $\log_{10} \varepsilon$ 3·12).

zwitterions (V), (VI), and (VII). The considerations outlined above render the site of the proton in (V) and (VI) fairly certain, but the structure (VII) is tentative. From the data available it is not possible to calculate the concentrations of the zwitterions in the different cases, but a consideration of the separation of the basic and acidic pK_a values in each case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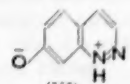
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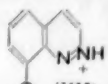
(VII)

suggests that the zwitterion concentration is greatest in the case of 6-hydroxycinnoline, a deduction which is supported by the relatively high intensity of the long-wavelength maximum in this case, and which conforms with the greater resonance stabilisation to be expected in the form (V).

5-Hydroxycinnoline appears to be slightly less basic than cinnoline. The significance of this fact is not at present clear. The wide separation of the two pK_a values for this compound, and the close similarity in neutral solution of the ultraviolet extinction curves of 5-hydroxy- and 5-methoxy-cinnoline make it very unlikely that appreciable zwitterion formation occurs in this case (insolubility makes the extension of the extinction curve difficult). The fact that the hydroxyl group is in the *peri*-position may result in a decrease in electromeric interaction with the nucleus, such as was observed with 5-aminocinnoline (preceding paper).

EXPERIMENTAL

6-Chlorocinnoline.—**4** : 6-Dichlorocinnoline (2·1 g.), toluene-*p*-sulphonhydrazide (3·9 g.), and dry chloroform (60 c.c.) were heated under reflux for 4 hr. The solution reddened and a deep-red solid separated. The mixture was set aside overnight, the chloroform was evaporated, and the slightly sticky residue was added during 10 min. to anhydrous sodium carbonate (40 g.) in water (400 c.c.) at 95°. The solution was boiled under reflux for 1 hr. and then extracted with ether. The red solid recovered from the ether was extracted (Soxhlet) with light petroleum (b. p. 60—80°). The extract was filtered (charcoal) and concentrated, the almost pure product (1·07 g.) separating. 6-Chlorocinnoline formed pale yellow needles, m. p. 131—131·5° (Found : C, 58·6; H, 3·1. Calc. for $C_8H_5N_2Cl$: C, 58·4; H, 3·1%), from light petroleum (b. p. 60—80°). Schofield and Swain [17] gave m. p. 119—120° for an impure specimen.

[17] Schofield and Swain, *J.*, 1950, 392.

7-Chlorocinnoline.—In the same way 4 : 7-dichlorocinnoline (1·8 g.) gave *7-chlorocinnoline* (0·55 g.), which formed felted pale yellow needles, m. p. 89—90° (Found : C, 58·9; H, 3·3%).

8-Chlorocinnoline.—4 : 8-Dichlorocinnoline (1·1 g.) appeared to react more slowly than its isomers, and refluxing was carried on for 6 hr. No solid separated, but removal of the chloroform gave a product which in the usual way provided *8-chlorocinnoline* (0·53 g.). This formed pale yellow crystals, m. p. 88—89° (Found : C, 58·6; H, 3·2%). A mixture with 7-chlorocinnoline showed m. p. *ca.* 50°.

Ionisation Constants.—The hydroxy-compounds (0·001 or 0·002M) in 0·01M-perchloric acid were titrated at 20° ± 0·05° with 0·04M-sodium hydroxide from a semimicro-burette. Measurements of pH were made with a Cambridge instrument and a glass electrode.

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812. *The Synthesis of* 3 : 4- *and* 5 : 6-*Benzophenanthridines.*

By B. MILLS and K. SCHOFIELD.

1-*o*-Acylaminoarylnaphthalenes have been cyclised to give 5 : 6-benzophenanthridine and some of its mono- and di-methyl derivatives. Acyl derivatives of *trans*-2-1′-naphthyl*cyclo*hexylamine could not be so cyclised. Anils of 2-hydroxymethylene-1-tetralone were converted into tetra(?)hydro-1 : 2 : 8 : 9-dibenzacridine by hot formic acid. 3-Acetyl-4-phenyl- and -*o*-tolyl-quinoline were prepared.

1-Phenyl-, 1-*p*-tolyl-, and 1-*o*-tolyl-2-tetralone have been prepared from the related epoxides. The oximes of the first two of the ketones were converted into 1-phenyl- and 1-*p*-tolyl-2-naphthylamine, acyl derivatives of which have been cyclised to give 3 : 4-benzophenanthridines.

NEITHER 5 : 6-benzophenanthridine (I; R = R′ = R″ = H) nor any of its derivatives have previously been described, and little is known about the 3 : 4-benzophenanthridines (II; R = R′ = H).[1] We have attempted to synthesise examples of these tetracyclic compounds because of their relation to the stereochemically interesting 3 : 4-benzophenanthrenes.[2]

5 : 6-Benzophenanthridines.—Hollingsworth and Petrow[3] obtained tetrahydrophenanthridines by cyclising with hot formic acid the anils derived from 2-hydroxymethylene-*cyclo*hexanone and aniline, α- and β-naphthylamine, and 3-aminoacenaphthene. Although the reaction failed with substituted anilines there was no obvious reason why the alicyclic portion of the anil should not be varied, and by application to 2-phenyliminomethyl-1-tetralone (III) the method might have given 5 : 6-benzophenanthridine.

Von Auwers and Wiegand[4] described 2-phenyliminomethyl-1-tetralone as a yellow compound, m. p. 117—119°, but in following their method we obtained from the reaction between aniline and 2-hydroxymethylene-1-tetralone two distinct substances. One of these was orange (m. p. 76—78°) and one yellow (m. p. 132—135°), and examination suggests that they are merely polymorphic forms of (III). Their ultraviolet absorption spectra were substantially identical and their reactions the same (see Experimental section). The anils from 2-hydroxymethylene-1-tetralone and *o*- and *p*-toluidine, *p*-anisidine, and β-naphthylamine were obtained only as yellow forms.

With hot formic acid all of these anils gave as the only homogeneous product a poor yield of the same compound, which could be dehydrogenated to a cream-coloured substance,

[1] Allen, "Six-Membered Heterocyclic Nitrogen Compounds with Four Condensed Rings," Interscience Publ., New York, 1951, p. 139; Walker, *J. Amer. Chem. Soc.*, 1954, **76**, 3999.
[2] Newman and Wheatley, *J. Amer. Chem. Soc.*, 1948, **70**, 1913.
[3] Hollingsworth and Petrow, *J.*, 1948, 1537.
[4] Von Auwers and Wiegand, *J. prakt. Chem.*, 1932, **134**, 82.

m. p. 189°. This differed from 5 : 6-benzophenanthridine, m. p. 109—110°, synthesised by an unambiguous method (see below). The formation, from the dehydrogenation product, of a readily decomposed *scarlet* picrate eliminated any alternative benzophenanthridine type of structure and from its ultraviolet absorption spectrum (Fig. 1) the product was recognised as 1 : 2 : 8 : 9-dibenzacridine (IV), and proved identical with an authentic specimen.[5] The initial product of the reaction is presumably a di- or tetra-hydro-1 : 2 : 8 : 9-dibenzacridine. How such a structure is produced is not clear. With hot formic acid 2-α- and 2-β-naphthyliminomethyl-1-tetralone gave merely small yields of 1- and 2-formamidonaphthalene respectively.

Encouraged by the efficient cyclisation achieved [6] with 2-formamidodiphenyl we next considered the use of 1-*o*-acylaminophenylnaphthalenes as sources of 5 : 6-benzophenanthridines. The method was successful but suffers from the inaccessibility of 1-*o*-nitroarylnaphthalenes,[7] for the Ullmann reactions by which these were obtained gave very poor yields with increased scale. The derived amines [1-*o*-aminophenyl-, 1-(2-amino-4-methylphenyl)-, and 1-(2-amino-6-methylphenyl)-naphthalene [7]] were readily acetylated and formylated. Many cyclisation experiments were carried out with 1-*o*-acetamidophenylnaphthalene, the best yield (39%) of 9-methyl-5 : 6-benzophenanthridine (I; R′ = R″ = H, R = Me) being obtained by using a mixture of phosphorus oxychloride and stannic chloride. The appropriate acyl compounds provided 2 : 9- (I; R = R′ = Me, R″ = H) and 4 : 9-dimethyl-5 : 6-benzophenanthridine (I; R = R″ = Me, R′ = H).

In contrast to these cyclisations of acetamido-compounds (which gave yellow reaction solutions), those of formamido-compounds quickly led to very deep red solutions. However, by using short reaction times, moderate to poor yields of 5 : 6- (I; R = R′ = R″ = H), 2-methyl-5 : 6- (I; R = R″ = H, R′ = Me), and 4-methyl-5 : 6-benzophenanthridine (I; R = R′ = H, R″ = Me) were obtained.

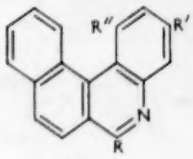
The difficulty of preparing 1-*o*-acylaminophenylnaphthalenes in quantity suggested the study of 1-amino-2-α-naphthyl*cyclo*hexane (V). 4-α-Naphthyl-5-nitro*cyclo*hexene was readily obtained from 1-2′-vinylnaphthalene [8] and butadiene, and reduced to 1-α-naphthyl-2-nitro*cyclo*hexane. With hydrogen and Raney nickel this gave the amine as a yellow oil which provided homogeneous acetyl and benzoyl derivatives. Analogy [9] suggests that the 1-2′-nitrovinylnaphthalene used in these experiments is the *trans*-isomer, and consequently the established stereochemical course of Diels–Alder reactions indicates *trans*-configurations for this 2-α-naphthyl*cyclo*hexylamine, its acetyl and benzoyl derivatives, and its precursors. As expected,[10] the *trans*-amine gave with phthalic anhydride the imide rather than the phthalamic acid. Reduction of *trans*-1-α-naphthyl-2-nitro*cyclo*hexane with lithium aluminium hydride, and subsequent acetylation, gave a mixture of isomers which could not be separated in practicable amounts. One isomer was identical with *trans*-1-acetamido-2-α-naphthyl*cyclo*hexane already mentioned, and the other was obviously the *cis*-isomer.[11]

Attempts to cyclise *trans*-1-acetamido- or *trans*-1-benzamido-2-α-naphthyl*cyclo*hexane with a number of reagents failed, and the azomethine formed from the amine and formaldehyde was merely hydrolysed under Pictet–Spengler conditions. These failures may be due to the *trans*-configuration of the amine, the known stereochemical oddness of α-naphthyl*cyclo*hexane derivatives,[12] or the insufficient activation of the naphthalene nucleus, although the successful cyclisation [13] of *N*-formyl-1-methyl-2-phenylpropylamine makes the last possibility unlikely.

cis-2-α-Naphthyl*cyclo*hexylamine would probably be obtainable through 2-α-naphthyl-*cyclo*hexanone, but no practicable synthesis of this ketone has been reported.[14]

[5] Senier and Austin, *J.*, 1906, 1396.
[6] Ockenden and Schofield, *J.*, 1953, 717.
[7] Forrest and Tucker, *J.*, 1948, 1137; Tucker and Whalley, *J.*, 1949, 3213.
[8] Mayer and Sieglitz, *Ber.*, 1922, **55**, 1835.
[9] Goebel and Wenzke, *J. Amer. Chem. Soc.*, 1938, **60**, 697.
[10] Klyne, "Progress in Stereochemistry," Butterworths, London, 1954, p. 63.
[11] Wildman and Norton, *J. Amer. Chem. Soc.*, 1954, **76**, 152.
[12] Cook and Lawrence, *J.*, 1936, 1431; Klemm and Hodes, *J. Amer. Chem. Soc.*, 1951, **73**, 5181.
[13] Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 1424.
[14] Orchin, *ibid.*, 1948, **70**, 495; Huang, *J. Org. Chem.*, 1954, **19**, 1363.

4-α-Naphthyl-5-nitro*cyclo*hexene gave no ketonic product in the Nef reaction (other failures with unsaturated compounds have been reported [15]), but 1-α-naphthyl-2-nitro-*cyclo*hexane provided moderately good yields of 2-α-naphthyl*cyclo*hexanone. Unfortunately, equal success was not achieved on the large scale.



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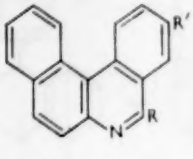

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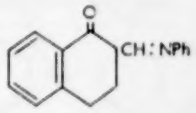

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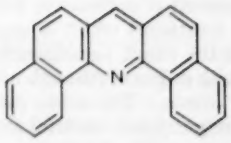

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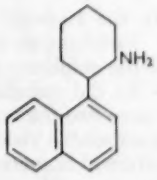

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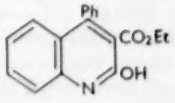

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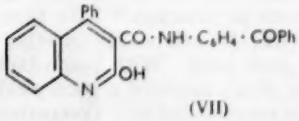


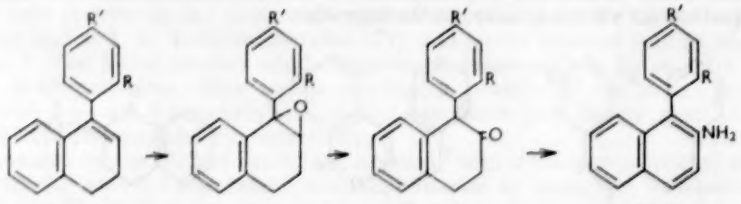
(VII)

One other approach to the 5 : 6-benzophenanthridine skeleton not yet successfully concluded deserves mention. We hoped to cyclise 4-phenyl-3-quinolylacetic acid. This might have been obtained from 4-phenylquinoline-3-carboxylic acid, prepared by Borsche and Sinn [16] in several stages from ethyl 2-hydroxy-4-phenylquinoline-3-carboxylate (VI). This ester was synthesised from ethyl malonate and *o*-aminobenzophenone, a later set of conditions [16b] being said to avoid formation of the anilide (VII) met in the earlier method.[16a] The original method gave us small yields of (VII) only, and the later conditions left the amine unchanged. By combining the two sets of conditions we obtained very good yields of the ester (VI) on several occasions, but, returning to the reaction later with different specimens of the reactants, inexplicably and despite repeated efforts we could isolate nothing but the amide (VII). This prevented us from completing the proposed synthesis, but with the available material we improved the preparation of 4-phenylquinoline-3-carboxylic acid. The acid chloride failed to undergo the Arndt–Eistert reaction, but by a malonic ester synthesis it provided 3-acetyl-4-phenylquinoline. In the Kindler–Willgerodt reaction this gave an unidentified product. 3-Acetyl-4-*o*-tolylquinoline was also prepared, but its use awaits clarification of the phenyl series. 3′-Oxoindeno(2′ : 1′-3 : 4)quinoline, obtained from 4-phenylquinoline-3-carboxylic acid, gave with diazomethane [17] 7(or 8)-methoxy-5 : 6-benzophenanthridine, isolated as its picrate. The yield did not encourage further examination of the reaction.

3 : 4-*Benzophenanthridines.*—Because of our success in cyclising 1-*o*-acylaminophenylnaphthalenes we examined the similar use of 2-acylamino-1-arylnaphthalenes. Zaugg, Freifelder, and Horrom [18] prepared 1-phenyl-2-naphthylamine (XI; R = R′ = H) from

[15] Tamelen and Thiede, *J. Amer. Chem. Soc.*, 1952, **74**, 2615.
[16] Borsche and Sinn, (*a*) *Annalen*, 1937, **532**, 146, (*b*) 1939, **538**, 283.
[17] Schutz, Schutz, and Cochran, *J. Amer. Chem. Soc.*, 1940, **62**, 2902; Badger, Carruthers, and Cook, *J.*, 1952, 4996.
[18] Zaugg, Freifelder, and Horrom, *J. Org. Chem.*, 1950, **15**, 1197.

3 : 4-dihydro-1-phenylnaphthalene by the processes (VIII—XI), and the ready availability of 1-aryl-3 : 4-dihydronaphthalenes made this an attractive route.



(VIII) (IX) (X) (XI)

Using the original conditions [18] in the 1-phenyl series we obtained a crude ketone which boiled over a very wide range. Variations in the amount of perbenzoic acid used in the initial step, and even omission of the sulphuric acid treatment which is supposed to isomerise the (oily) epoxide (IX ⟶ X), did not change the result significantly. In all cases distillation of the crude ketone gave two fractions with different (though not sharply separated) boiling ranges but giving comparable yields of oxime. The oxime melted over a wide range and may have been a mixture of isomers. Frequent and wasteful recrystallisation was required to produce a specimen with m. p. comparable to that reported by Zaugg *et al.*

With epoxidations in chloroform, the solvent used in the earlier work,[18] there is a tendency for aromatic rings to be attacked.[19] We therefore carried out the oxidation, (VIII; R = R′ = H) ⟶ (IX; R = R′ = H), in ether and thus obtained the epoxide in crystalline form and in good yield. With boron trifluoride–ether complex the solid epoxide gave a crude ketone which provided a good yield of oxime (again wide-melting), but which boiled over a wide range as before. Comparison of boron trifluoride and dilute sulphuric acid showed the former to be preferable for forming the ketone. A similar series of experiments were carried through with 3 : 4-dihydro-1-*p*-tolylnaphthalene. The oxime of 1-*p*-tolyl-2-tetralone so obtained was more nearly homogeneous than the phenyl compound and more easily purified.

3 : 4-Dihydro-1-*o*-tolylnaphthalene (VIII; R = Me, R′ = H) (now obtained satisfactorily from α-tetralone and *o*-tolyl-lithium—the Grignard reagent gives unsatisfactory results [20]) was epoxidised considerably more slowly than the phenyl or the *p*-tolyl compound. The oily epoxide was converted into 1-*o*-tolyl-2-tetralone (X; R = Me, R′ = H) but in no circumstances could more than a trace of the oxime be obtained from this ketone although the enol-acetate was prepared. The behaviour of the ketone recalls that of 4-*tert.*-butyl-3 : 4-dihydro-2-hydroxy-1-naphthyl mesityl ketone.[21]

With acetic anhydride, pyridine, and acetyl chloride,[22] 1-phenyl- and 1-*p*-tolyl-2-tetralone oxime gave good yields of 2-diacetylamino-1-phenyl- and -1-*p*-tolyl-naphthalene. The derived amines were easily monoacetylated and monoformylated. The small available quantity of 1-*o*-tolyl-2-tetralone oxime gave no recognisable product in attempts to aromatise it.

Phosphorus oxychloride–stannic chloride converted 2-acetamido-1-phenyl- and -1-*p*-tolyl-naphthalene into 9-methyl- (II; R = Me, R′ = H) and 7 : 9-dimethyl-3 : 4-benzophenanthridine (II; R = R′ = Me), respectively, in moderate yields. In this series the formamido-compounds behaved like the 1-*o*-formamidoarylnaphthalenes mentioned above, and from them only small yields of 7-methyl-3 : 4-benzophenanthridine (II; R = H, R′ = Me) and 3 : 4-benzophenanthridine (II; R = R′ = H) were isolable.

In this series also an attempt was made to extend the method of Hollingsworth and

[19] Gutsche and Fleming, *J. Amer. Chem. Soc.*, 1954, **76**, 1771.
[20] Friedel, Orchin, and Reggel, *ibid.*, 1948, **70**, 199; 1951, **73**, 1449.
[21] Fuson and Fang, *ibid.*, 1955, **77**, 3781.
[22] Beringer and Ugelow, *ibid.*, 1953, **75**, 2635.

Petrow,[3] but with hot formic acid the anil derived from β-naphthylamine and 2-hydroxymethylene-6-methyl*cyclo*hexanone gave only 2-formamidonaphthalene. Repetition of this method for preparing **5 : 6 : 7 : 8**-tetrahydro-**3 : 4**-benzophenanthridine is described below.

FIG. 1. **1 : 2 : 8 : 9-***Dibenzacridine* **(1); 3 : 4-***benzophenanthridine* **(2).**

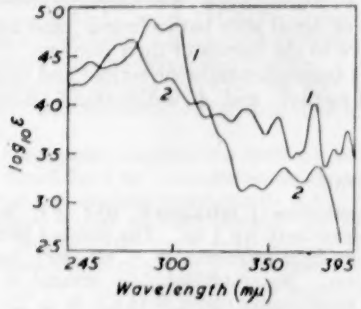
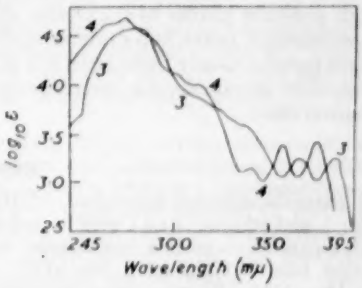


FIG. 2. **4-***Methyl-* **(3),** *and* **9-***methyl-***5 : 6-***benzophenanthridine* **(4).**



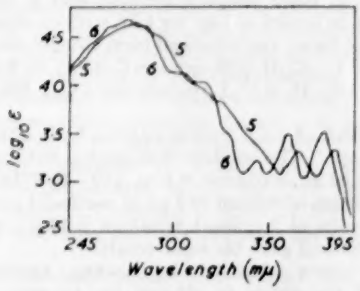


FIG. 3. **4 : 9-***Dimethyl-* **(5),** *and* **2 : 9-***dimethyl-***5 : 6-***benzophenanthridine* **(6).**

Ultraviolet absorption spectra *(in absolute ethanol).**

Compound	$\lambda_{max.}$ (mμ)								$\log_{10} \varepsilon_{max.}$							
5 : 6-Benzophenanthridine																
Unsubstd.	—	272	*283*	*308*	*315*	*326*	341	358	376	—	4·57	*4·44*	*3·9*	*3·83*	*3·43*	3·04	3·26	3·30
2-Methyl-	—	273	*284*	*305*	*317*	*328*	344	361	379	—	4·69	*4·61*	*4·03*	*3·96*	*3·56*	3·27	3·48	3·52
4-Methyl-	—	278	*291*	*313*	*339*	—	—	366	384	—	4·58	*4·43*	*3·87*	*3·57*	—	—	3·25	3·26
9-Methyl-	*266*	273	*284*	*301*	*316*	—	341	357	375	*4·61*	4·66	*4·55*	*4·12*	*3·98*	—	3·16	3·38	3·42
2 : 9-Dimethyl-	—	276	*286*	*302*	*316*	*328*	343	360	378	—	4·66	*4·59*	*4·13*	*4·02*	*3·51*	3·21	3·46	3·51
4 : 9-Dimethyl-	—	280	*296*	*316*	*325*	—	—	366	384	—	4·62	*4·42*	*3·95*	*3·81*	—	—	3·31	3·31
3 : 4-Benzophenanthridine																
Unsubtd.	*269*	278	297	314	*326*	341	358	375	—	*4·58*	4·65	4·27	4·02	*3·61*	3·16	3·36	3·37	—
9-Methyl-	*272*	278	298	314	*328*	*343*	356	374	—	*4·63*	4·66	4·34	4·11	*3·82*	*3·19*	3·41	3·45	—
7 : 9-Dimethyl-	—	276	296	314	328	343	356	374	—	—	4·62	4·24	4·06	3·65	3·18	3·43	3·47	—
1 : 2-8 : 9-Dibenzacridine	256	288	302	324	337	354	364	374	—	4·44	4·86	4·82	3·90	3·95	3·86	3·50	4·0	
	384	391								3·54	3·73							
Di(?)hydro-1 : 2-8 : 9-dibenzacridine	245	280	292	*302*	*326*	335				4·38	3·91	3·85	*3·58*	*4·09*	4·12			

* Figures in italics refer to shoulders or inflexions.

All of the **3 : 4-** and **5 : 6**-benzophenanthridines now synthesised exhibited characteristic blue fluorescence in solution. In the **3 : 4**-benzophenanthrene series[2] the 5-methyl derivatives show m. p.s considerably higher than those of the other members, and in contrast do not form picrates. With the **5 : 6**-benzophenanthridines the 4-methyl and the **4 : 9**-dimethyl compound melt considerably higher than the parent and the other monomethyl derivatives, but so does **2 : 9**-dimethyl-**5 : 6**-benzophenanthridine. All these

compounds formed stable picrates, which like those of the 3 : 4-benzophenanthridines were very insoluble. (It is obvious from the work of Petrow [23] and of Hollingsworth and Petrow [3] and from our own experiments that in the report by Kenner, Ritchie, and Wain [24] the m. p.s of benzophenanthridines and benzacridines became transposed.)

The ultraviolet extinction curve of 5 : 6-benzophenanthridine is almost identical with those of the 2- and 9-methyl, and 2 : 9-dimethyl derivatives (see Figures and Table). In contrast, the extinction curves of 4-methyl- and 4 : 9-dimethyl-5 : 6-benzophenanthridine, though generally similar to the others, show loss of detail with bathochromic, and for the long-wavelength peaks hypochromic shifts relative to the curves of their isomers. These changes parallel closely those observed in the 3 : 4-benzophenanthrene series [2] and indicate considerable intramolecular overcrowding in 4-methyl- and 4 : 9-dimethyl-5 : 6-benzophenanthridine.

Experimental

2-Phenyliminomethyl-1-tetralone.—2-Hydroxymethylene-1-tetralone [25] (0·2 g.), aniline (0·12 g.), and ethanol (1 c.c.) were heated on the steam-bath for ½ hr. The product (0·25 g.) which separated on cooling was digested with boiling light petroleum (b. p. 60—80°), leaving a yellow solid (0·1 g.; m. p. 105—112°) undissolved. Recrystallised from ethanol it gave m. p. 130—133°. Evaporation of the extract gave small orange plates (0·14 g.), m. p. 72—74°.

The same quantities of reagents left for 24 hr. at room temperature gave 0·01 g. of the orange substance and 0·19 g. of the yellow compound, or heated at 150° for ½ hr. without ethanol, 0·15 g. of the former, and 0·06 g. of the latter. These *forms*, recrystallised from ethanol, formed orange needles, m. p. 72—75° (Found : C, 81·8; H, 6·1. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·0%), and yellow needles, m. p. 131—133° (Found : C, 81·6; H, 6·5%), respectively ($\lambda_{max.}$ 262 and 400 mμ; $\log_{10}\varepsilon$ 4·23 and 4·45).

The lower-melting form of the anil (1 g.), ethanol (3 c.c.), hydroxylamine hydrochloride (1·4 g.), and water (2 c.c.) were set aside for 16 days. The solution was diluted with water and extracted with ether. The dried extract provided an *iso*oxazole,[26] b. p. 180—184°/14 mm. This (0·3 g.) in ether (5 c.c.) was added to a cold solution of sodium (0·2 g.) in methanol (2 c.c.). After 12 hr. the solution was concentrated, fine needles of 2-cyano-1-tetralone (0·17 g.), m. p. 72—75°, separating. The higher-melting form of the anil gave the same result.

2-Aryliminomethyl-1-tetralones.—The following were obtained by boiling equivalent quantities of 2-hydroxymethylene-1-tetralone and the amine in ethanol for 15 min., and recrystallising the products from ethanol : 2-p-*Tolyl-* (55%), orange needles, m. p. 144—145° (Found : C, 82·2; H, 6·1. $C_{18}H_{17}ON$ requires C, 82·1; H, 6·5%), 2-o-*tolyl-* (62%), yellow needles, m. p. 76—78° (Found : C, 82·1; H, 6·1%), 2-p-*methoxyphenyl-* (60%), yellow needles, m. p. 89—91° (Found : C, 77·3; H, 6·0. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1%), and 2-α-*naphthyl-iminomethyl-1-tetralone* (98%), yellow needles, m. p. 122—124° (Found : C, 83·9; H, 5·8. $C_{21}H_{17}ON$ requires C, 84·25; H, 5·7%).

Treatment of 2-Aryliminomethyl-1-tetralones with Formic Acid.—2-Phenyliminomethyl-1-tetralone (1 g.) and 96% formic acid (100 c.c.) were refluxed for 36 hr. The resulting red solution, which showed a strong green fluorescence, was concentrated at reduced pressure, and the residue was basified and extracted with ether. Evaporation of the dried (Na_2SO_4) extract and recrystallisation of the product from ethanol gave yellow crystals (0·4 g.). In subsequent experiments the yield was always much lower. In the same way the *o*-tolyl (0·47 g.), *p*-tolyl (0·5 g.), and *p*-methoxyphenyl analogues (0·5 g.) gave the same product (0·06, 0·09, and 0·04 g. respectively). *Tetra(?)hydro-1 : 2 : 8 : 9-dibenzacridine* formed yellow plates or needles, m. p. 159—160° (Found : C, 89·4; H, 6·3; N, 4·8. $C_{21}H_{17}N$ requires C, 89·0; H, 6·05; N, 4·9%), from ethanol.

This compound was heated with an equal weight of palladium–charcoal (30%) for 2 hr. under nitrogen at 250°. Sublimation and recrystallisation from acetone gave pale cream needles of 1 : 2 : 8 : 9-dibenzacridine, m. p. 189—190° (Found : C, 89·0; H, 4·7; N, 5·2. Calc. for $C_{21}H_{13}N$: C, 90·3; H, 4·7; N, 5·0%), which showed a strong, almost purple fluorescence

[23] Petrow, *J.*, 1942, 693.
[24] Kenner, Ritchie, and Wain, *J.*, 1937, 1526.
[25] Ott and Tarbell, *J. Amer. Chem. Soc.*, 1952, **74**, 6269.
[26] von Auwers and Rold, *J. prakt. Chem.*, 1937, **150**, 57; Johnson and Shelberg, *J. Amer. Chem. Soc.*, 1945, **67**, 1745.

in acetone and a pale blue fluorescence in concentrated sulphuric acid, and was identical (mixed m. p.) with an authentic specimen. The picrate, which easily dissociated, crystallised from a small volume of acetone as scarlet needles, m. p. 193—194°, alone and mixed with an authentic specimen.

1-o-*Acylaminophenylnaphthalenes.*—1-*o*-Aminophenylnaphthalene (1·46 g.) and formic acid (70 c.c.) were refluxed for 6 hr. Removal of the acid at reduced pressure, and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave needles of 1-o-*formamidophenylnaphthalene* (1·31 g.), m. p. 121—123° (Found : C, 82·3; H, 5·7. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3%). Similarly, 1-(2-amino-6-methylphenyl)- (0·6 g.) and 1-(2-amino-4-methylphenyl)-naphthalene (0·2 g.) gave, respectively, 1-(2-*formamido-6-methylphenyl*)- (0·52 g.), needles, m. p. 131—133° (Found : C, 82·0; H, 5·9. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8%), and 1-(2-*formamido-4-methylphenyl*)-*naphthalene* (0·2 g.), needles, m. p. 155—157° (Found : C, 82·7; H, 5·8%).

1-*o*-Aminophenylnaphthalene (0·49 g.), acetic anhydride (0·5 g.), and dry benzene (5 c.c.) were refluxed for 4 hr. Concentration at reduced pressure and crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave needles (0·16 g.) of 1-o-*acetamidophenylnaphthalene*, m. p. 95—96° (Found : C, 81·8; H, 5·8. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8%). Similarly, the appropriate amines (0·26 and 0·2 g. respectively) gave 1-(2-*acetamido-6-methylphenyl*)- (0·25 g.), m. p. 104—105° (Found : C, 82·8; H, 6·2. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2%), and 1-(2-*acetamido-4-methylphenyl*)-*naphthalene*, needles (0·21 g.), m. p. 127—128° (Found : C, 82·85; H, 6·2%), from benzene.

5 : 6-*Benzophenanthridines.*—The following conditions, the most satisfactory of many used, illustrate the general method. 1-*o*-Acetamidophenylnaphthalene (0·64 g.), phosphorus oxychloride (20 c.c.), and anhydrous stannic chloride (0·96 g.) were refluxed for 8 hr. Most of the phosphorus oxychloride was then removed at reduced pressure and the chilled residue was treated with water and aqueous ammonia. Extraction with benzene gave a product which from benzene–light petroleum formed pale yellow prisms (0·23 g.) of 9-*methyl-5 : 6-benzophenanthridine*, m. p. 93—94° (Found : C, 88·7; H, 4·9; N, 5·7. $C_{18}H_{13}N$ requires C, 88·9; H, 5·35; N, 5·8%). Prepared in alcohol, and recrystallised from 2-ethoxyethanol, the *picrate* formed yellow needles, m. p. 210—215° (decomp.) (Found : C, 61·2; H, 3·5; N, 12·5. $C_{18}H_{13}N,C_6H_3O_7N_3$ requires C, 61·0; H, 3·4; N, 11·9%).

The conditions used in other cases are tabulated.

1-Arylnaphthalene	Wt. (g.)	$POCl_3$ (c.c.)	$SnCl_4$ (g.)	Time	Yield (g.)	Product
o-Formamidophenyl	0·5	10	1·06	4 hr.	0·08	*a*
2-Formamido-4-methylphenyl	0·1	5	0·2	10 min.	0·02	*b*
2-Formamido-6-methylphenyl	0·2	5	0·4	3 hr.	0·06	*c*
2-Acetamido-4-methylphenyl	0·55	30	1·07	5 hr.	0·14	*d*
2-Acetamido-6-methylphenyl	0·2	8	0·28	8 hr.	0·06	*e*

The picrates of the products were all prepared in alcohol and recrystallised from 2-ethoxyethanol. The products were :

(*a*) 5 : 6-*Benzophenanthridine*, needles, m. p. 109—110° (Found : C, 89·1; H, 5·0. $C_{17}H_{11}N$ requires C, 88·45; H, 5·1%), from acetone. *Picrate*, yellow needles, m. p. 253—255° (Found : C, 60·0; H, 3·0; N, 13·4. $C_{17}H_{11}N,C_6H_3O_7N_3$ requires C, 60·3; H, 2·8; N, 12·2%).

(*b*) 2-*Methyl*-5 : 6-*benzophenanthridine*, prisms, m. p. 115—116° (Found : C, 88·9; H, 5·45. $C_{18}H_{13}N$ requires C, 88·9; H, 5·4%), from benzene–light petroleum (b. p. 60—80°).

(*c*) 4-*Methyl*-5 : 6-*benzophenanthridine*, prisms, m. p. 180—182° (Found : C, 87·4; H 5·6%), from acetone. *Picrate*, yellow needles, m. p. 220° (Found : C, 61·6; H, 3·4. $C_{18}H_{13}N,C_6H_3O_7N_3$ requires C, 61·0; H, 3·4%).

(*d*) 2 : 9-*Dimethyl*-5 : 6-*benzophenanthridine*, yellow needles, m. p. 171—172° (Found : C, 88·0; H, 5·7. $C_{19}H_{15}N$ requires C, 88·7; H, 5·9%), from benzene–light petroleum (b. p. 60—80°). *Picrate*, yellow needles, m. p. 264° (Found : C, 61·8; H, 3·9; N, 11·7. $C_{19}H_{15}N,C_6H_3O_7N_3$ requires C, 61·7; H, 3·7; N, 11·5%).

(*e*) 4 : 9-*Dimethyl*-5 : 6-*benzophenanthridine*, yellow needles, m. p. 150—151° (Found : C, 88·7; H, 4·9%), from ether–light petroleum (b. p. 60—80°). *Picrate*, yellow needles, m. p. 230° (Found : C, 61·9; H, 3·8%).

4-α-*Naphthyl-5-nitrocyclohexene.*—1-2′-Nitrovinylnaphthalene (7·5 g.), butadiene (6·1 g.), toluene (10 c.c.), and a trace of quinol were heated in a sealed tube (evacuated to 30 mm. pressure) for 2 days at 100°. The cold tube was opened and excess of butadiene was removed by gentle heating, the toluene was evaporated, and the residue was recrystallised

from ethanol, giving pale yellow needles of 4-α-*naphthyl*-5-*nitro*cyclo*hexene* (4·9 g.), m. p. 124—125° (Found : C, 76·0; H, 6·0; N, 5·3. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0; N, 5·5%). The yield varied from 52% to 62%.

trans-1-α-*Naphthyl*-2-*nitro*cyclo*hexane*.—The above compound (9·8 g.), acetic acid (300 c.c.), and platinum oxide (0·4 g.) were shaken with hydrogen. Reduction was complete in 2½ hr., then the mixture was filtered and concentrated. From methanol the residual oil gave needles (8·7 g.) of trans-1-α-*naphthyl*-2-*nitro*cyclo*hexane*, m. p. 96—98° (Found : C, 74·7; H, 6·8; N, 5·4. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%).

trans-2-α-*Naphthyl*cyclo*hexylamine*.—The nitro-compound (4 g.) in ethanol was reduced with hydrogen in the presence of Raney nickel (20 c.c. of settled suspension). Reduction was complete in 5 hr., and, in the usual way, the amine (2·3 g.) was isolated as a pale yellow viscous oil, b. p. 160—164°/0·05 mm.

The amine (0·2 g.), acetic anhydride (0·14 g.), and dry pyridine were heated at 100° for 3 hr. The solution was poured into water, and the product (0·19 g.) crystallised from benzene, giving small needles of trans-1-*acetamido*-2-α-*naphthyl*cyclo*hexane*, m. p. 178—179° (Found : C, 80·6; H, 7·7. $C_{18}H_{21}ON$ requires C, 80·9; H, 7·9%).

In the same way the amine (0·2 g.), benzoyl chloride (0·14 g.), and pyridine (5 c.c.) gave the *benzamido-compound* (0·25 g.) which separated from ethanol as needles, m. p. 192—193° (Found : C, 83·5; H, 7·2. $C_{23}H_{23}ON$ requires C, 83·2; H, 7·3%).

When the amine (0·2 g.) and phthalic anhydride (0·13 g.) were refluxed for 7 hr. in chlorobenzene (5 c.c.) removal of the solvent at reduced pressure gave an oil which solidified on trituration with benzene–light petroleum (b. p. 60—80°). Crystallisation from acetone gave prisms (0·12 g.) of trans-2-α-*naphthyl*-1-*phthalimido*cyclo*hexane*, m. p. 192—194° (Found : C, 80·9; H, 5·9. $C_{24}H_{21}O_2N$ requires C, 81·1; H, 6·0%).

Lithium Aluminium Hydride Reduction of trans-1-α-*Naphthyl*-2-*nitro*cyclo*hexane*.—The nitro-compound (3 g.) in ether (90 c.c.) was added dropwise to a gently refluxing solution of lithium aluminium hydride (1·4 g.) in ether (100 c.c.). After refluxing for 4 hr. the mixture was treated with water and dilute aqueous sodium hydroxide. Thorough extraction with ether and evaporation of the dried (Na_2SO_4) extract gave an oil (2·1 g.) which was heated for 3 hr. at 100° with acetic anhydride (1·43 g.) and pyridine (30 c.c.). The acetylation solution was decomposed with water and extracted with ether. Drying (Na_2SO_4), evaporation, and removal *in vacuo* of the last traces of pyridine gave an oil from which, on addition of ether, a solid (1·62 g.), m. p. 144—146°, separated. (Concentration of the ethereal layer gave 0·24 g. of an oil, probably unchanged amine.) The solid was crystallised three times from benzene, and the more soluble fractions were combined and passed in benzene over alumina. The first two fractions (0·13 g.), m. p. 181—183°, gave no m. p. depression when mixed with the acetyl derivative prepared from the Raney nickel reduction product. The last two fractions (0·05 g.) were recrystallised from benzene, giving needles of the cis-*acetamido-compound*, m. p. 182—185° (Found : C, 80·6; H, 7·9%), which gave a strong m. p. depression when mixed with the *trans*-compound.

2-α-*Naphthyl*cyclo*hexanone*.—1-α-Naphthyl-2-nitro*cyclo*hexane (0·5 g.) in absolute ethanol (20 c.c.) was treated with a solution of sodium (0·1 g.) in ethanol (5 c.c.) and set aside for 1 hr. under nitrogen. The pale green solution was added dropwise to concentrated hydrochloric acid (8 c.c.), water (30 c.c.), and ethanol (25 c.c.) under nitrogen at 0° and stirred for 1½ hr. at this temperature. After being stirred for 8 hr. at room temperature the yellow solution was diluted with water and extracted with ether. Evaporation of the dried (Na_2SO_4) extract gave an oil (0·4 g.) which was heated for 10 min. on the steam-bath with semicarbazide hydrochloride (0·5 g.), and sodium acetate (1 g.) in water with sufficient ethanol to ensure homogeneity. Chilling the solution gave 2-α-naphthyl*cyclo*hexanone semicarbazone (0·34 g., 64%), m. p. 208—210° (Found : C, 72·5; H, 6·8; N, 13·6. Calc. for $C_{17}H_{19}ON_3$: C, 72·6; H, 6·8; N, 14·9%), which formed fawn needles from ethanol. Orchin [14] gave m. p. 213—215°. This yield could not be attained in larger-scale experiments.

Ethyl 2-*Hydroxy*-4-*phenylquinoline*-3-*carboxylate*.—*o*-Aminobenzophenone (15 g.) and ethyl malonate (30 g.) were heated together at 175—180° for 2 hr. Recrystallised from ethanol the product gave prisms (62%) of ethyl 2-hydroxy-4-phenylquinoline-3-carboxylate, m. p. 196—198°. Experiments on one-third of this scale gave 89% of the ester.

Ethyl 2-*Hydroxy*-4-*o*-*tolylquinoline*-3-*carboxylate*.—2-Amino-2′-methylbenzophenone (0·44 g.) and ethyl malonate were heated for 1 hr. at 175—180°. Crystallisation from ethanol gave prisms (0·41 g.) of *ethyl* 2-*hydroxy*-4-*o*-*tolylquinoline*-3-*carboxylate*, m. p. 171—173° (Found : C, 74·2; H, 5·7. $C_{19}H_{17}O_3N$ requires C, 74·3; H, 5·6%).

Ethyl 2-Chloro-4-phenylquinoline-3-carboxylate.—The hydroxy-compound (3·75 g.) and phosphorus oxychloride (11·3 c.c.) were refluxed for 1 hr. The solution was concentrated under reduced pressure and the residue was decomposed with ice and aqueous sodium hydroxide and extracted with ether. Evaporation of the dried (Na_2SO_4) extract gave the *chloro-compound* (3·05 g.), which formed yellow needles, m. p. 104—106° (Found: C, 69·6; H, 4·6; N, 4·3. $C_{18}H_{14}O_2NCl$ requires C, 69·3; H, 4·5; N, 4·5%), from ethanol.

Ethyl 2-Chloro-4-o-tolylquinoline-3-carboxylate.—In the same way the hydroxy-*o*-tolyl compound (2·3 g.) gave the *chloro-compound* (1·4 g.), which formed plates, m. p. 121—123° (Found: C, 70·4; H, 5·0. $C_{19}H_{16}O_2NCl$ requires C, 70·0; H, 5·0%), from ethanol.

4-Phenylquinoline-3-carboxylic Acid.—Ethyl 2-chloro-4-phenylquinoline-3-carboxylate (3 g.), red phosphorus (1·5 g.), and hydriodic acid (12 c.c.; *d* 1·7) were refluxed together for 8 hr. Most of the hydriodic acid was then removed, and the residue was thoroughly extracted with boiling aqueous sodium carbonate. The extract was just acidified (Congo-red) with hydrochloric acid, boiled, and filtered hot. The cooled filtrate was treated with sodium acetate, and the product was crystallised from acetic acid. It formed needles (2·15 g.), m. p. 228—230°.

4-o-Tolylquinoline-3-carboxylic Acid.—The chloro-compound (1·2 g.), hydriodic acid (9·6 c.c.), and red phosphorus (0·6 g.) were refluxed for 7 hr. The mixture was worked up as before and the product was precipitated by bringing the alkaline extract to pH 5—6 with hydrochloric acid. The *acid* (0·77 g.) formed needles, m. p. 235—236° (Found: C, 74·0; H, 5·2. $C_{17}H_{13}O_2N,H_2O$ requires C, 75·0; H, 5·2%), from acetic acid.

3-Acetyl-4-phenylquinoline.—The acid chloride prepared from 4-phenylquinoline-3-carboxylic acid (2·5 g.) and thionyl chloride was suspended in dry benzene (40 c.c.) and added rapidly to ethyl sodiomalonate (from 4·75 g. of the ester) in benzene (100 c.c.). The mixture was refluxed for ½ hr., treated with water, and extracted with benzene. Evaporation of the extract gave a small amount of an oil. Neutralisation of the aqueous layer gave the ether-soluble product, which on crystallisation from ethanol provided pale yellow needles (1·3 g.) of *ethyl 4-phenyl-3-quinolylcarbonylmalonate*, m. p. 106—107° (Found: C, 70·9; H, 5·4. $C_{23}H_{21}O_5N$ requires C, 70·6; H, 5·4%). A similar experiment with 4 g. of the acid gave 3·3 g. of product.

When the quinoline acid (0·5 g.) was treated as above but the solution obtained on decomposition with water was left overnight before being worked up, long, crisp needles (0·33 g.) of a *product*, m. p. 193—200° (decomp.) (Found: C, 63·5; H, 5·2. $C_{21}H_{17}O_5N,2H_2O$ requires C, 63·2; H, 5·3%), separated from the aqueous layer. It was probably a dihydrate of the half ester of 4-phenyl-3-quinolylcarbonylmalonic acid.

Ethyl 4-phenyl-3-quinolylcarbonylmalonate (2·21 g.) and 20% sulphuric acid (100 c.c.) were refluxed together for 3 hr. The cooled solution was basified and extracted with ether. The dried (Na_2SO_4) extract gave on evaporation *3-acetyl-4-phenylquinoline* which separated as yellow needles (1·15 g.), m. p. 76—78° (Found: C, 82·7; H, 5·2. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3%), from light petroleum (b. p. 60—80°).

When this ketone (1·15 g.), sulphur (0·46 g.), and morpholine (6 c.c.) were refluxed for 13 hr. and the solution was poured into ethanol, an orange solid separated. This *substance* formed orange needles (0·8 g.), m. p. 202—204° (Found: C, 65·0; H, 5·6; N, 8·3%), from ethanol. Attempts to hydrolyse the product with mixtures of acetic acid and sulphuric acid were unsuccessful.

3-Acetyl-4-o-tolylquinoline.—To ethyl sodiomalonate (from 0·37 g. of the ester) in benzene (15 c.c.), 4-*o*-tolylquinoline-3-carboxylic acid chloride (from 0·2 g. of the acid) in benzene (15 c.c.) suspension was added rapidly, and the mixture was refluxed for 1 hr. Water was added and the aqueous layer was separated. Neutralisation gave no organic material. The benzene layer was concentrated and shaken with dilute hydrochloric acid. Ether was added, and the organic layer was separated, dried (Na_2SO_4), and evaporated, leaving a reddish oil (0·17 g.) which could not be crystallised. This oil (0·59 g.) and 20% sulphuric acid (30 c.c.) were refluxed for 4 hr. The yellow solution was decanted from some black oil, cooled, basified, and extracted with ether. The dried (Na_2SO_4) extract provided an oil (0·34 g.) which from light petroleum (b. p. 40—60°) gave yellow prisms of *3-acetyl-4-o-tolylquinoline*, m. p. 92—94° (Found: C, 82·7; H, 5·4; N, 5·3. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8; N, 5·4%).

7(or 8)-Methoxy-5 : 6-benzophenanthridine.—3′-Oxoindeno(2′ : 1′-3 : 4)quinoline[1] (0·31 g.) and ethereal diazomethane (*ca.* 20 equivs.) were set aside for 16 hr. at 5°. After 36 hr. more at room temperature the solution was concentrated at reduced pressure, giving a brown gum (0·27 g.). Passage in benzene over alumina gave a sticky solid which darkened in air and showed blue fluorescence in benzene. With picric acid in ethanol it gave *7(or 8)-methoxy-5 : 6-benzophenanthridine picrate* which separated as a bright yellow powder (0·1 g.), m.p. 224—232°

(decomp.) (Found: C, 59·1; H, 3·5. $C_{18}H_{13}ON,C_6H_3O_7N_3$ requires C, 59·0; H, 3·3%), from 2-ethoxyethanol.

1-*Phenyl*-2-*tetralone*.—(*a*) Perbenzoic acid (8·3 g.) in ether (135 c.c.) was added with stirring to 3 : 4-dihydro-1-phenylnaphthalene (11·25 g.) in ether (100 c.c.) at such a rate that the temperature did not rise above −2°. After being stirred for 9 hr. at 0° (preliminary titrations showed that the consumption of perbenzoic acid was almost complete in this time) the solution was washed with dilute aqueous sodium hydroxide and with water and then dried (Na_2SO_4). 3 : 4-*Dihydro*-1-*phenylnaphthalene epoxide* (7·5 g.) formed needles, m. p. 100—102° (Found: C, 86·9; H, 6·2. $C_{16}H_{14}O$ requires C, 86·5; H, 6·4%), from benzene–light petroleum (b. p. 60—80°).

The epoxide (3·2 g.) in dry ether (30 c.c.) was treated with boron trifluoride–ether complex (2·54 g.). After the initial exothermic reaction the brown solution was set aside for 17 hr. before being washed with dilute aqueous sodium hydroxide and water. The dried (Na_2SO_4) extract gave on evaporation and distillation a yellow oil (1·44 g.), b. p. 156—164°/2 mm., and a dark yellow oil (0·53 g.), b. p. 174—210°/2 mm. These fractions gave the oxime (see below) in comparable yields.

(*b*) A chloroform solution of the peracid was added slowly to 3 : 4-dihydro-1-phenylnaphthalene in chloroform, below −4°. The solution was then stirred at 0° for 2½ hr., washed with dilute aqueous sodium hydroxide and water, and dried (Na_2SO_4). After removal of the chloroform the oil was either distilled at once, or boiled with 30% sulphuric acid before being distilled. Some results are tabulated.

	Dihydro-cpd. in $CHCl_3$		Peracid in $CHCl_3$		Acid	Product	
Expt.	(g.)	(c.c.)	(g.)	(c.c.)	treatment	g.	b. p.
A	2·8	25	2·08	40	None	1·05	146—150°/0·5 mm.
						0·49	180—190°/ ,,
B	,,	,,	,,	,,	Given	1·12	150—154°/0·6 mm.
						0·62	160—184°/ ,,
C	2·26	30	2·28	44	None	1·01	150—154°/0·5 mm.
						0·69	174—210/ ,,
D	13·07	100	9·6	105	None	4·45	140—146°/0·1 mm.
						2·77	156—178°/ ,,

A portion of the lower-boiling oil from expt. D which had been set aside for a long time at a temperature of *ca.* 10° gave crystals of the somewhat impure ketone, m. p. 39—41° (Found: C, 85·3; H, 6·1. Calc. for $C_{16}H_{14}O$: C, 86·5; H, 6·4%).

1-*Phenyl*-2-*tetralone Oxime*.—In all cases the ketone and 10 equivs. of hydroxylamine hydrochloride were refluxed in ethanol containing enough sodium hydroxide to make the solution alkaline. Usually the oxime separated in 10 min. The mixture was cooled in ice and the product was collected.

(*a*) From the ketone prepared from crystalline epoxide: The ketone (0·16 g.), b. p. 156—164°/2 mm., gave the oxime (0·12 g.), m. p. 162—174°. The crude ketone (2·65 g.) obtained directly from boron trifluoride rearrangement of the epoxide gave the oxime (2·1 g.), m. p. 162—173°.

(*b*) From the ketone prepared from the product of epoxidation in chloroform: In each experiment 1 g. of the oils obtained in the experiments described above was converted into oxime, which melted in the range 160—170° (see Table). The lower-boiling oil from expt. D

	Yield of oxime (g.)	
Expt.	From lower-boiling oil	From higher-boiling oil
A	0·75	1·0
B	—	0·95
C	0·75	0·68
D	0·54	0·56

(3·77 g.) gave the oxime (3·1 g.), m. p. 162—174°. Several crystallisations from ethanol gave plates, m. p. 178—180° (Found: C, 80·9; H, 6·4. Calc. for $C_{16}H_{15}ON$: C, 80·3; H, 6·4%).

1-p-*Tolyl*-2-*tetralone*.—(*a*) Perbenzoic acid (4·56 g.) in ether (110 c.c.) was added to a stirred solution of 3 : 4-dihydro-1-*p*-tolylnaphthalene (6·57 g.) in ether (100 c.c.) at −5°. Stirring was continued for 9 hr. at 0°. In the usual way the epoxide (7·2 g.) was isolated as a pale yellow oil. Distillation caused much decomposition but by this means a somewhat impure specimen, b. p. 146—148°/1 mm. (Found: C, 87·5; H, 7·0. Calc. for $C_{17}H_{16}O$: C, 86·4; H, 6·8%), was obtained. It did not react with hydroxylamine. In another experiment the ethylene (11·3 g.) gave 12·1 g. of crude epoxide.

The epoxide (11·8 g.) in ether (25 c.c.) was treated with boron trifluoride–ether complex (7·08 g.) at room temperature. After the initial reaction the solution was set aside for 18 hr. at room temperature, washed with dilute alkali and water, and dried (Na_2SO_4). Evaporation and distillation gave a yellow oil (2·93 g.), b. p. 185—195°/0·6 mm.

A similar experiment with 1 g. of epoxide in boiling benzene gave 0·94 g. of crude ketone.

(*b*) 3 : 4-Dihydro-1-*p*-tolylnaphthalene (9·4 g.) in chloroform (75 c.c.) was treated at −6° with perbenzoic acid (6·25 g.) in chloroform (134 c.c.). After being stirred for 3 hr. at 0° the solution was worked up as before to give (i) a solid (0·42 g.), b. p. 150—158°/10 mm., which furnished needles, m. p. 120—120·5° (Found: C, 65·5; H, 7·6%), from ethanol, (ii) a pale yellow oil (4·5 g.), b. p. 150—156°/0·4 mm., and (iii) a yellow viscous oil (1·36 g.), b. p. 172—178°/0·4 mm. The last two fractions both gave the oxime.

1-p-*Tolyl-2-tetralone Oxime.*—(*a*) The lower-boiling oil (2·7 g.) from the boron trifluoride rearrangement gave the crude oxime (2·2 g.), m. p. 164—168°. Recrystallisation from ethanol gave needles (0·92 g.), m. p. 169—171°, and the pure *oxime* showed m. p. 170—172° (Found: C, 81·2; H, 6·8. $C_{17}H_{17}ON$ requires C, 80·7; H, 6·9%). The higher-boiling oil (2·93 g.) gave 2·83 g. of crude material, and after crystallisation 1·38 g., m. p. 170—172°.

(*b*) The undistilled oil (0·9 g.) from an oxidation in chloroform gave 0·34 g. of crude oxime. In another experiment the oil (4·5 g.) gave finally 2·49 g. of pure oxime, m. p. 170—172°.

3 : 4-*Dihydro*-1-*o-tolylnaphthalene.*—α-Tetralone (20 g.) in ether (100 c.c.) was added slowly to a stirred solution of *o*-tolyl-lithium (from 70 g. of *o*-bromotoluene and 5·7 g. of lithium) in ether (300 c.c.). After being refluxed gently for 16 hr. the mixture was decomposed with ice and dilute hydrochloric acid, the ether layer was separated, and the aqueous layer was thoroughly extracted with ether. Evaporation of the combined, dried (Na_2SO_4) extracts and refluxing of the residual oil with concentrated hydrochloric acid (3 c.c.) in benzene (100 c.c.) gave a product which on distillation provided the dihydro-compound as a pale yellow oil (16·1 g.), b. p. 119—120°/0·2 mm. (Found: C, 93·5; H, 7·2. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). This crystallised, and from light petroleum (b. p. 60—80°) gave massive, crisp rhombs, m. p. 53—55°. Heated with 30% palladium–charcoal at 150—160° for 2 hr., it gave 1-*o*-tolylnaphthalene, needles (from methanol), m. p. 61—63°. This compound strongly depressed the m. p. of the dihydro-compound when mixed with it.

1-o-*Tolyl-2-tetralone.*—To a solution of 3 : 4-dihydro-1-*o*-tolylnaphthalene (7·43 g.) in ether (50 c.c.), perbenzoic acid (5·13 g.) in ether (84 c.c.) was added with stirring, at −3° to −5°. After being stirred for 10 hr. at this temperature the solution was kept at 5° for 13 hr. and at room temperature for 3½ hr. (In parallel experiments it was found that at 0° 3 : 4-dihydro-1-phenylnaphthalene consumed 80% of the theoretical amount of perbenzoic acid in 8½ hr., whilst the *o*-tolyl compound required 22 hr. to reach this figure.) The crude epoxide (7·1 g.) was isolated as a clear yellow oil. This oil (6·74 g.) in anhydrous benzene (30 c.c.) was warmed on the steam-bath and boron trifluoride–ether complex (4·05 g.) in benzene (10 c.c.) was added cautiously. After 10 min. the benzene solution was washed with aqueous sodium hydroxide and with water, dried (Na_2SO_4), and evaporated, giving a viscous yellow oil (3·29 g.), b. p. 246—252°/0·8 mm. Redistillation gave 1-o-*tolyl-2-tetralone* (2·1 g.) as a sweet-smelling, yellow oil, b. p. 149—151°/0·4 mm. (Found: C, 85·8; H, 6·9. $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%).

The ketone (0·42 g.), hydroxylamine hydrochloride (1·18 g.), 2N-sodium hydroxide (9 c.c.), and ethanol (6 c.c.) were refluxed for ½ hr. The chilled solution was extracted with ether. The oil obtained from the dried extract was dissolved in the minimum volume of ethanol; on cooling, the *oxime* (0·06 g.) separated as plates, m. p. 145—147° (Found: C, 80·7; H, 6·8%).

The ketone (0·5 g.), anhydrous sodium acetate (1 g.), and acetic anhydride (5 c.c.) were heated on the steam-bath for 62 hr. The solution was poured into water and the precipitated oil was extracted with ether. Drying (Na_2SO_4) and evaporation gave an oil which from light petroleum (b. p. 60—80°) provided needles of the *enol acetate* (0·1 g.), m. p. 97—99° (Found: C, 82·1; H, 6·6. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

1-*Phenyl-2-naphthylamine.*—1-Phenyl-2-tetralone oxime and 1 equiv. of pyridine in a large excess of acetic anhydride were kept in the refrigerator for 24 hr. Acetyl chloride (1 equiv.) was added and the solution was heated at 100° for 1 hr. Most of the solvent was removed at reduced pressure and water was added. The oil was dried (Na_2SO_4) in ether and crystallised from ethanol, to give needles of 2-diacetamido-1-phenylnaphthalene, m. p. 107—108° (Found: C, 78·4; H, 5·5. Calc. for $C_{20}H_{17}O_2N$: C, 79·2; H, 5·6%). From uncrystallised oxime (0·5, 0·27, 0·27 g.) the yields were 27, 21, and 22%. With once crystallised oxime (0·42, 0·31, 1·96 g.) yields were 65, 50, and 60%.

Hydrolysis of the diacetyl compound (1·8 g.) with boiling 1 : 1 aqueous hydrochloric acid

(10 c.c.) for 3½ hr. gave a crystalline hydrochloride. The base was liberated with ammonia, extracted with ether, and crystallised from light petroleum (b. p. 40—60°), giving fawn needles (0·83 g.) of 1-phenyl-2-naphthylamine, m. p. 93—94°. Heated with excess of anhydrous formic acid for 1 hr. at 100° this gave 2-*formamido*-1-*phenylnaphthalene* which formed prisms (70%), m. p. 121—123° (Found : C, 83·0; H, 5·7. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3%), from ethanol. Refluxing the amine with acetic anhydride (1·3 mols.) in benzene for 3 hr. gave 2-*acetamido*-1-*phenylnaphthalene* (100%) which formed rosettes of needles, m. p. 132—134° (Found : C, 82·5; H, 5·7. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8%), from benzene–light petroleum (b. p. 60—80°).

1-p-*Tolyl*-2-*naphthylamine*.—By the above method the appropriate pure oxime (1·38, 1·38, 0·8 g.) gave 2-*diacetamido*-1-p-*tolylnaphthalene* (65, 70, and 66%) which separated from ethanol as plates, m. p. 123—124° (Found : C, 79·4; H, 6·0. $C_{21}H_{19}O_2N$ requires C, 79·5; H, 6·0%). Hydrolysis as before gave 1-p-*tolyl*-2-*naphthylamine* (74%) which formed needles, m. p. 134—136° (Found : C, 87·4; H, 6·5. $C_{17}H_{15}N$ requires C, 87·5; H, 6·5%), from light petroleum (b. p. 60—80°). 2-*Formamido*-1-p-*tolylnaphthalene* separated from ethanol as prisms (83%), m. p. 160—162° (Found : C, 82·6; H, 6·1. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8%), and 2-*acetamido*-1-p-*tolylnaphthalene* from aqueous ethanol as prisms (83%), m. p. 125—126° (Found : C, 82·7; H, 6·2. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2%).

3 : 4-*Benzophenanthridine*.—(*a*) 2-Formamido-1-phenylnaphthalene (0·1 g.), phosphorus oxychloride (5 c.c.), and stannic chloride (0·16 g.) were refluxed for 1 hr. Excess of phosphorus oxychloride was removed at reduced pressure, and the dark red residue was basified and extracted with chloroform. The oil obtained from the chloroform gave, with picric acid in ethanol, 3 : 4-benzophenanthridine picrate which separated as a yellow powder, m. p. 229—233° (decomp.) (Found : C, 59·7; H, 3·1. Calc. for $C_{17}H_{11}N,C_6H_3O_7N_3$: C, 60·2; H, 3·1%), from 2-ethoxyethanol.

(*b*) 2-β-Naphthyliminomethyl*cyclo*hexanone (10 g.) was refluxed with formic acid (100 c.c.) for 20 hr. and worked up as usual. The resulting oil was treated with picric acid in ethanol, and the picrate was digested with hot ethanol, giving a brown powder (6·9 g.), m. p. 243—247°. The free base, liberated by lithium hydroxide, separated from light petroleum (b. p. 60—80°) as pale brown needles (2·82 g.), m. p. 92—95°. This (0·8 g.) and 30% palladium–charcoal (0·4 g.) were heated at 310—320° for 6 hr. under nitrogen. Crystallisation from benzene–light petroleum, short-path distillation, and recrystallisation gave a mixture of plates and needles, m. p. 105—106°.

9-*Methyl*-3 : 4-*benzophenanthridine*.—2-Acetamido-1-phenylnaphthalene (0·52 g.), phosphorus oxychloride (25 c.c.), and stannic chloride (0·75 g.) were refluxed for 2½ hr. 9-*Methyl*-3 : 4-*benzophenanthridine* was obtained as needles (0·42 g.), m. p. 105—107° (Found : C, 86·7; H, 5·7. $C_{18}H_{13}N,\frac{1}{2}H_2O$ requires C, 86·7; H, 5·5%). The *picrate*, m. p. 238° (decomp.) (Found : C, 60·2; H, 3·2. $C_{18}H_{13}N,C_6H_3O_7N_3$ requires C, 61·0; H, 3·4%), formed bright yellow needles from 2-ethoxyethanol.

7-*Methyl*-3 : 4-*benzophenanthridine*.—2-Formamido-1-*p*-tolylnaphthalene (0·1 g.), phosphorus oxychloride (5 c.c.), and stannic chloride (0·15 g.) were refluxed for 10 min. Processing as in the previous case gave an oil (0·05 g.) which provided the *picrate*, forming small yellow needles, m. p. 280° (decomp.) (Found : C, 62·5; H, 3·2. $C_{18}H_{13}N,C_6H_3O_7N_3$ requires C, 61·0; H, 3·4%), from 2-ethoxyethanol.

7 : 9-*Dimethyl*-3 : 4-*benzophenanthridine*.—As for the 9-methyl compound, 2-acetamido-1-*p*-tolylnaphthalene (0·43 g.), phosphorus oxychloride (30 c.c.), and stannic chloride (0·53 g.) provided 7 : 9-*dimethyl*-3 : 4-*benzophenanthridine*, which formed needles (0·36 g.), m. p. 96—98° (Found : C, 83·0; H, 6·3. $C_{19}H_{15}N,H_2O$ requires C, 82·9; H, 6·2%), from benzene–light petroleum. The *picrate*, m. p. 250° (Found : C, 61·4; H, 3·0%), gave yellow needles from the usual solvent.

2-*Methyl*-6-β-*naphthyliminomethyl*cyclo*hexanone*.—2-Hydroxymethylene-6-methyl*cyclo*hexanone (1 g.), β-naphthylamine (1·02 g.), and ethanol (5 c.c.) were refluxed for 20 min. The anil separated on cooling and formed yellow needles (1·8 g.), m. p. 125—127°, from ethanol. When this was treated with formic acid in the usual way only a small amount of 2-formamidonaphthalene, m. p. 127—129°, was recovered.

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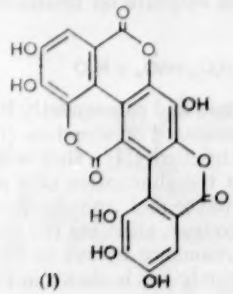
813. *Flavogallol.*

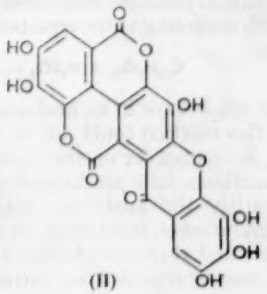
By J. Grimshaw and R. D. Haworth.

Structure (I), considered but rejected by earlier workers, is now proposed for flavogallol. The properties of the compound are satisfactorily accounted for on the basis of this structure (I) which has been confirmed by rational synthesis.

During experiments on the oxidation of hydroxybenzoic acids, Bleuler and A. G. Perkin [1] isolated flavogallol from the products of the action of arsenic acid on gallic acid in sulphuric acid solution, and made an extensive study of its reactions. Flavogallol is a hexahydric phenol of molecular formula, $C_{21}H_8O_{12}$, characterised as the hexa-acetate, the hexabenzoate, and, in the present work, the hexamethyl ether. Bleuler and Perkin concluded that flavogallol contained two lactone groups, and as ellagic acid is a by-product of its formation they suggested that flavogallol possessed structure (I) or (II). In their view, structure (II) accorded better with its properties but until now no further evidence has been brought forward to support either formulation.

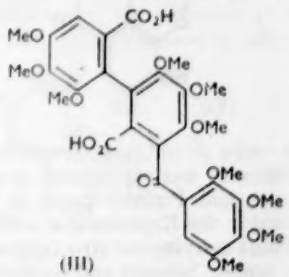


(I)

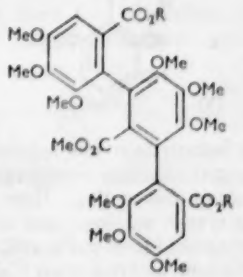


(II)

Evidence for the presence of two lactone rings was obtained by exhaustive treatment of flavogallol with methyl sulphate and an excess of aqueous alkali. This afforded two isomeric acids, $C_{19}H_2O(OMe)_{10}(CO_2H)_2$, further characterised as their dimethyl esters. The acids were not readily interconverted but on demethylation both gave flavogallol, identified as its hexa-acetate. Bleuler and Perkin considered that structure (I) would give a tribasic acid containing nine methoxyl groups and therefore concluded that this evidence



(III)



(IV)

supported structure (II), from which a dibasic acid (III) containing ten methoxyl groups would be expected if the reaction conditions may be assumed to be sufficiently vigorous to rupture the phenolic ether link. Their objection to formula (I) is however invalid, for the

[1] Bleuler and Perkin, *J.*, 1916, **109**, 529.

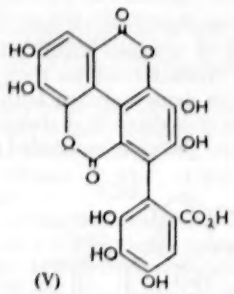
product here would be expected to be the dibasic acid (IV; R = H) because of the difficulty of hydrolysis of 2 : 6-disubstituted benzoic esters. The difficulty of hydrolysis and re-esterification of such benzoic esters is well known, and later two cases closely analogous to (IV) will be cited. Derivatives of the acid (IV) can exist in *meso*- and racemic forms, owing to restricted rotation about the diphenyl links, thus explaining the isomerisation encountered.

One of the lactone rings in flavogallol is extremely unstable and may be opened under conditions which do not affect coumarin itself. Bleuler and Perkin termed the resulting parent compound, $C_{20}H_2O_4(OH)_7{\cdot}CO_2H$, flavogallonic acid, and its decarboxylation product flavogallone. Flavogallonic acid was re-lactonised only on dissolution in sulphuric acid or on acetylation, when it furnished hexa-*O*-acetylflavogallol. Acetylation of flavogallonic esters gave the corresponding esters of hepta-*O*-acetylflavogallonic acid and we have now prepared methyl hepta-*O*-methylflavogallonate. An explanation of this instability is not readily apparent from structure (II). However, the steric crowding of structure (I) will result in the non-planar arrangement of one lactone ring which in consequence will be weakened, and give rise to structure (V) for flavogallonic acid containing an unstrained arrangement of lactone rings.

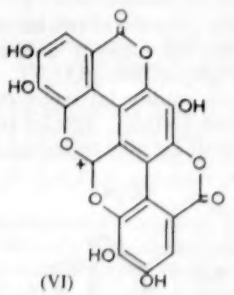
Besides giving a series of alkali-metal salts, flavogallol also behaved as an anhydro-base, yielding the orange, crystalline anhydro-hydrogen sulphate on treatment with sulphuric acid in acetic acid, according to the equation :

$$C_{21}H_8O_{12} + H_2SO_4 \longrightarrow C_{21}H_7O_{11}{\cdot}HSO_4 + H_2O$$

Ellagic acid does not behave in an analogous manner and consequently Bleuler and Perkin considered that this reaction could not be accommodated on structure (I). In their view it could only be accounted for on the xanthone structure (II); they overlooked the fact, however, that xanthone salts are formed without the elimination of a molecule of water demanded to satisfy the analytical data on flavogallol anhydro-hydrogen sulphate. Structure (I) may, however, function as an anhydro-base, affording the cation (VI) which is completely planar and therefore stabilised as a resonance hybrid to which a number of canonical forms may be regarded as contributing [only one is shown in (VI)].



(V)



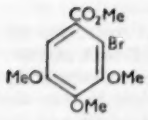
(VI)

Evidently more information was required in order to settle the constitution of flavogallol. For this re-investigation considerable difficulty was experienced in repeating the original preparation of flavogallol. Here Bleuler and Perkin's paper is incoherent—possibly part of the text is missing—and we record in the Experimental section a method for preparing the compound from gallic acid. Whilst carrying out structural investigations on valoneic acid dilactone, isolated from *Valonea* tannin, Schmidt and Komarek [2] prepared a xanthone to which they assigned structure (II), stating that it appeared not to be identical with flavogallol. Direct comparison of hexa-*O*-methylvaloneaxanthone and hexa-*O*-methylflavogallol has confirmed this; the two compounds differ in m. p., mixed m. p., and infrared absorption spectrum. Both compounds show a band at 1745 cm.$^{-1}$

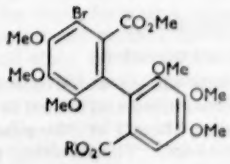
[2] Schmidt and Komarek, *Annalen*, 1955, **591**, 156.

(lactone-carbonyl) but only the valoneaxanthone has a band at 1664 cm.$^{-1}$ (benzophenone-type carbonyl). In addition, it has been shown that the hexamethyl ether of flavogallol may be oxidised to 3 : 4 : 5-trimethoxyphthalic acid; this observation cannot be accommodated on structure (II) but is quite in accord with structure (I) for flavogallol. As we have shown, structure (I) accounts for the properties of flavogallol and its correctness has now been demonstrated by rational synthesis.

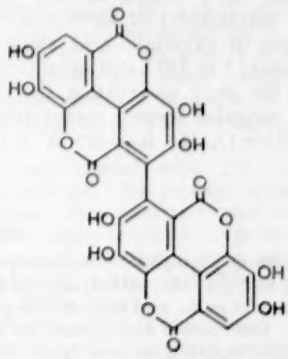
An obvious route to the ester (IV; R = Me), intermediate in a synthesis of flavogallol, is by the Ullmann reaction between the esters (VII) and (VIII; R = Me). In preliminary experiments, the action of copper powder on the gallic acid derivative (VII) alone was examined. This route to the corresponding hexamethoxydiphenic ester does not appear to have been previously recorded and the product is usually prepared from ellagic acid.[3] The new route is very convenient, for it avoids working with the very insoluble ellagic acid and its tetramethyl ether. Successive bromination of the hexamethoxydiphenic ester furnished its mono- (VIII; R = Me) and di-bromo-derivative (X). The mixture of di-



(VII)



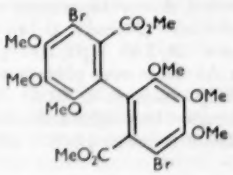
(VIII)



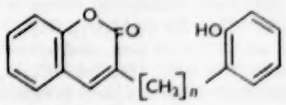
(IX)

and ter-phenyls resulting from the Ullmann reaction between the bicyclic ester (VIII; R = Me) and an excess of the monocyclic ester (VII) was separated by distillation. Saponification of the oily terphenyl fraction gave an acidic mixture from which no crystalline material other than a trace of the hexamethoxydiphenic acid could be isolated. However, demethylation of the remainder afforded flavogallol which did not give the Griessmayer test for ellagic acid and was identified as its hexa-acetate, hexabenzoate, and hexamethyl ether, thus establishing structure (I) for the phenol.

For completeness the Ullmann product from the bromodiphenyl (VIII) alone was examined. On demethylation it afforded "dehydrodiellagic acid" (IX), where the

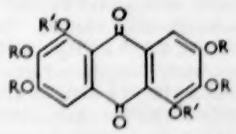


(X)



(XI): $n = 1$

(XII): $n = 0$

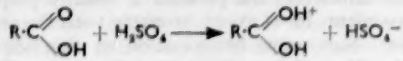


(XIII)

arrangement of lactone rings is probably as shown since any other grouping would introduce strain due to steric crowding and so be less stable. This phenol gave the Griessmayer reaction and was further distinguished from flavogallol by its great insolubility and the properties of its octa-acetate and octamethyl ether.

[3] Herzig and Pollak, *Monatsh.*, 1908, **29**, 263; Schmidt and Demmler, *Annalen*, 1952, **576**, 85.

The compound (VIII; R = Me) possesses a 2 : 6-disubstituted benzoic ester group and, as expected, the major product of alkaline hydrolysis was the half-ester (VIII; R = H). Under the usual conditions of alkaline hydrolysis about half of the dibromo-ester (X) was recovered unchanged. These two examples are analogous to the difficultly hydrolysable ester group present in the degradation product (IV; R = H or Me). Unfortunately no simple analogue of the cation (VI) has been found which affords a crystalline salt under the conditions tried. Salts could not be prepared from the simpler coumarin analogues (XI) and (XII). Analogy may be drawn, however, between the cation (VI) and the protonation of carboxylic acids in sulphuric acid solution which has been investigated by cryoscopy [4] and proceeds according to the equation :



In the early stages of this work it was thought that rufigallol might be a possible contaminant of flavogallol. Rufigallol (XIII; R = R′ = H) is the product of the action of sulphuric acid alone on gallic acid.[5] Its structure was advanced by Klobukowski [6] in 1877 and since this date little further work has appeared. In order to confirm the early observation the compound was re-prepared. Purified *via* the hexa-acetate, rufigallol formed scarlet needles which with diazomethane furnished the tetramethyl ether (XIII; R = Me, R′ = H).

Experimental

M. p.s are corrected.

Isolation of Flavogallol.—Arsenic pentoxide (33 g.) was dissolved in water (85 ml.), 98% sulphuric acid (270 ml.) added, and the mixture stirred and heated in an oil-bath at 120°. After the addition of gallic acid hydrate (30 g.) during about ½ hr., the mixture was kept at 110—120° for 6 hr., then cooled and poured on crushed ice. The resulting precipitate was washed by decantation, centrifuged, and dried, first on a steam-bath in a current of air and finally at 130°/15 mm. A dark brown powder (24 g.) resulted which was heated with acetic anhydride (80 ml.) and pyridine (1 ml.) (vigorous initial reaction) for 3 hr., then allowed to cool overnight. The precipitate was collected, digested with hot acetic anhydride (600 ml.), cooled, and filtered. Evaporation of the filtrate to *ca.* 60 ml. caused the separation of hexa-*O*-acetylflavogallol (2—3 g.) which was filtered off when cold, and recrystallised from acetic anhydride as colourless needles, m. p. 290—292° (decomp.) (lit.,[1] m. p. 278—280°) (Found : C, 56·0, 56·1; H, 3·2, 3·2. Calc. for $C_{33}H_{30}O_{18}$: C, 56·25; H, 2·9%).

For hydrolysis, the hexa-acetate (1·0 g.) was dissolved in 98% sulphuric acid (10 ml.), kept at 55° for 3 hr., cooled and poured on crushed ice. Flavogallol was precipitated and was collected at the centifruge, washed repeatedly with water till free from acid, then dried in a desiccator, giving a greenish powder. Traces of sulphuric acid afforded an orange product. Crude flavogallol was dissolved in a minimum of hot dimethylformamide, and the solution rapidly cooled and diluted with an equal volume of water, the phenol slowly separating as greenish-yellow needles. When air-dried, flavogallol forms a trihydrate * (Found : C, 49·6, 50·1; H, 3·0, 3·1; H_2O, 10·5; N, 0. Calc. for $C_{21}H_{18}O_{12},3H_2O$: C, 49·8; H, 2·8; H_2O, 10·7%), completely dehydrated after 3 hr. at 130°/0·01 mm. and affording a *dihydrate* over phosphoric oxide at 18°/0·1 mm. (2 hr.) (Found : C, 51·8; H, 2·8. $C_{21}H_{18}O_{12},2H_2O$ requires C, 51·6; H, 2·5%). The anhydrous phenol was very hygroscopic; it rapidly increased in weight and after 1 hr. in air formed the dihydrate (Found : H_2O, 6·9. $C_{21}H_{18}O_{12},2H_2O$ requires H_2O, 7·4%) which very slowly re-formed the trihydrate.

Flavogallol was insoluble in all solvents except pyridine and dimethylformamide. With 2N-sodium hydroxide it gave an orange solution (distinction from ellagic acid) and with sulphuric acid a magenta-red solution from which acetic acid precipitated the orange anhydro-sulphate.

* Bleuler and Perkin's analyses fit a trihydrate; their calculated values for a tetrahydrate are in error.

[4] Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 52.
[5] Robiquet, *Annalen*, 1836, **19**, 204; Löwe, *J. prakt. Chem.*, 1869, **107**, 298.
[6] Klobukowski, *Ber.*, 1877, **10**, 885.

In dimethylformamide it gave an indigo-blue ferric test. In the Griessmayer reaction[7] it afforded a purple solution decolorised on addition of water (distinction from ellagic acid).

The hexabenzoate, prepared with benzoic anhydride and a trace of pyridine, and precipitated with benzene, separated from nitrobenzene as canary-yellow prisms, m. p. 326—328° (lit.,[1] m. p. 326—328°) (Found: C, 70·05; H, 3·1. Calc. for $C_{48}H_{32}O_{12}$: C, 70·25; H, 3·0%).

Hexa-O-methylflavogallol.—Methylation of flavogallol with ethereal diazomethane furnished the ***hexamethyl ether*** which crystallised from dimethylformamide as yellow needles, m. p. 328—330° (Found: C, 60·2; H, 4·1. $C_{27}H_{20}O_{12}$ requires C, 60·45; H, 3·8%), depressed by hexa-*O*-methylvalonea xanthone.[2] Hexa-*O*-methylflavogallol in a potassium bromide disc showed infrared bands at 1744, 1598, 1584, 1505, 1490, 1462, 1421, 1400, 1351, 1334, 1320, 1242, 1199, 1169, 1156, 1120, 1093, 1040, 1020, 990, 966, 955, 927, 904(s), 860(s), 790, 782, 772, 760(s), 752, and 743 cm.$^{-1}$. Hexa-*O*-methylvalonea xanthone as a similar disc had absorption bands at 1744, 1664, 1602, 1560(w), 1511(w), 1459, 1430, 1408, 1358, 1324, 1291, 1257, 1229, 1204, 1161, 1150, 1129, 1106, 1042, 1027, 993, 968, 938, 889(s), 750(s), and 740(s) cm.$^{-1}$.

A portion of the hexamethyl ether was treated with equivalent amounts of methyl sulphate and alkali according to the procedure of Schmidt and Komarek[3] for hexa-*O*-methylvalonea xanthone. The gummy ester product, on trituration with methanol, left a small amount of an insoluble residue which crystallised from chloroform–methanol as colourless needles, m. p. 275—277° [Found: OMe, 50·2. $C_{21}H_{12}O_4(OMe)_{10}$ requires OMe, 49·4%], probably a ***monolactonic dimethyl ester***. Evaporation of the filtrate followed by dilution with water precipitated one form of the ester (IV; R = Me), crystallising from aqueous methanol as needles, m. p. 128—129° (lit.,[1] m. p. 128—130°) (Found: C, 58·8; H, 5·9; OMe, 53·9. Calc. for $C_{32}H_{36}O_{15}$: C, 58·8; H, 5·6; 12OMe, 55·2%).

Methyl Hepta-O-methylflavogallonate.—Flavogallol was digested with 2% methanolic sulphuric acid (100 parts) for 2 hr., forming a colourless solution. Evaporation of the solvent and addition of water precipitated methyl flavogallonate. This ester re-formed flavogallol, identified as the hexamethyl ether, on dissolution in 98% sulphuric acid followed by precipitation with ice. With excess of ethereal diazomethane ***methyl hepta-O-methylflavogallonate*** was formed and crystallised from methanol as colourless needles, m. p. 242—244° (Found: C, 59·0; H, 4·8; OMe, 41·0. $C_{29}H_{28}O_{13}$ requires C, 58·8; H, 4·4; 8OMe, 42·6%).

Oxidation of Hexa-O-methylflavogallol.—Hexa-*O*-methylflavogallol (1·25 g.) was dissolved in a solution of potassium hydroxide (1·5 g.) in water (30 ml.), and the mixture cooled to room temperature. Finely powdered potassium permanganate (6·8 g.) was slowly added with occasional cooling; the rapid uptake ceased abruptly. The mixture was then diluted with water and filtered and the manganese dioxide washed with hot 2N-potassium hydroxide. The filtrates were combined, acidified with dilute sulphuric acid, and extracted with ether for 9 hr. Evaporation of the dried (Na_2SO_4) ethereal extract left a brown solid (0·19 g.) which sublimed at 160°(bath)/0·15 mm. as pale yellow needles (0·10 g.). This sublimate crystallised from ether as colourless silky needles, m. p. 143—144°, undepressed on admixture with 3 : 4 : 5-trimethoxyphthalic anhydride.[5] The anil[8] crystallised from 50% ethanol as needles, m. p. and mixed m. p. 144—145° (Found: N, 4·7. Calc. for $C_{17}H_{15}O_5N$: N, 4·5%).

Methyl 2-Bromo-3 : 4 : 5-trimethoxybenzoate.—Bromination of methyl 3 : 4 : 5-trimethoxybenzoate in carbon tetrachloride (after Hamburg[8a]) afforded material containing some 10—15% of unbrominated ester difficult to remove by distillation. Re-esterification of the pure acid, m. p. 150—151°, afforded the bromo-ester as a mobile oil, b. p. 119—120°/0·03 mm. (Found: C, 43·4; H, 4·4; Br, 26·1. Calc. for $C_{11}H_{13}O_5Br$: C, 43·3; H, 4·25; Br, 26·25%), which did not solidify. In the literature it is described as an oil,[8a] a solid[8b] of m. p. 90°, and a solid[8c] of m. p. 33°.

Dimethyl 2 : 3 : 4 : 2′ : 3′ : 4′-Hexamethoxy-6 : 6′-diphenate.—Crude methyl 2-bromo-3 : 4 : 5-trimethoxybenzoate (25 g.) was heated at 210—220° and copper bronze (15 g.) gradually stirred in. After 2 hr. the mixture was cooled, extracted with chloroform, and filtered. The filtrate was washed with water and sodium hydrogen carbonate solution and dried (Na_2SO_4) and the solvent removed. Distillation of the residue afforded (*a*) methyl 3 : 4 : 5-trimethoxybenzoate, b. p. 114—118°/0·1 mm. (2·75 g.), and (*b*) the dimethyl hexamethoxydiphenate, b. p. 192—195°/0·1 mm., which solidified and crystallised from aqueous methanol as stout needles (11 g.), m. p. 110—111°. Hydrolysis of a sample furnished the diphenic acid, needles (from aqueous

[7] Griessmayer, *Annalen*, 1871, **160**, 51.

[8] Bargellini and Molina, *Atti R. Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1912, **21**, II, 146.

[8a] (*a*) Hamburg, *Monatsh.*, 1898, **19**, 596; (*b*) Bogert and Plant, *J. Amer. Chem. Soc.*, 1915, **37**, 2726; (*c*) Feist and Dschu, *Festschrift für A. Tschirch* (*Leipzig*), 1926, 29; *Chem. Zentr.* 1927, II, 58.

ethanol), m. p. 242—243° undepressed by material of m. p. 239—240° prepared from ellagic acid.[3] It formed mixed crystals with tri-*O*-methylgallic acid, making their separation tedious.

Dimethyl 5-Bromo-2 : 3 : 4 : 2′ : 3′ : 4′-hexamethoxy-6 : 6′-diphenate (VIII; R = Me).—The above diphenic ester (10 g.) and iodine (0·05 g.) were dissolved in carbon tetrachloride (30 ml.); then bromine (3·6 g.) in carbon tetrachloride (30 ml.) was slowly added at room temperature. After 30 min., the mixture was washed successively with sodium sulphite solution, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated. Distillation afforded the crude monobromo-derivative, b. p. 218—220°/0·05 mm. (10 g.). Hydrolysis of the ester with 2N-methanolic potassium hydroxide for 1 hr. afforded the *hydrogen bromo-ester* (VIII; R = H), crystallising from 30% ethanol as stout needles, m. p. 190—191° (Found: C, 49·2; H, 4·6; Br, 15·1. $C_{31}H_{23}O_{16}Br$ requires C, 48·9; H, 4·45; Br, 15·5%); rapid cooling of solutions afforded an unstable dimorph as fine needles, m. p. 150—151°. Re-esterification of the pure acid afforded the pure *monobromo-ester* (VIII; R = Me), b. p. 219—220°/0·04 mm., a colourless glass (Found: C, 49·6; H, 4·9; Br, 14·8. $C_{32}H_{25}O_{16}Br$ requires C, 49·9; H, 4·7; Br, 15·1%). After some time it solidified and separated from dilute methanol as stout needles, m. p. 74—75°.

Dimethyl 5 : 5′-Dibromo-2 : 3 : 4 : 2′ : 3′ : 4′-hexamethoxy-6 : 6′-diphenate (X).—Treatment of the diphenic ester with 3 times the above quantity of bromine afforded the *dibromo-ester* (X), which separated from methanol as needles, m. p. 126—127° (Found: C, 43·45; H, 4·0; Br, 26·4. $C_{32}H_{24}O_{16}Br_2$ requires C, 43·4; H, 3·95; Br, 26·3%). After this ester (0·150 g.) had been refluxed with an excess of 10% methanolic potassium hydroxide for 90 min., 0·083 g. (55%) was recovered unchanged and a gummy acid fraction (0·056 g.; 37%) was formed.

" Dehydrodiellagic Acid " (IX).—Pure dimethyl 5-bromo-2 : 3 : 4 : 2′ : 3′ : 4′-hexamethoxy-6 : 6′-diphenate (2 g.) and copper bronze (2 g.) were heated at 220° for 1½ hr. with stirring; then the mixture was cooled and triturated with chloroform. Filtration and evaporation of the filtrate left a gum which was demethylated by 4 hours' refluxing with hydriodic acid (15 ml.; *d* 1·7) and acetic anhydride (5 ml.). The phenol was precipitated as an almost colourless powder (1·0 g.) which was collected and washed with dilute sulphurous acid and water. " Dehydrodiellagic acid " was almost insoluble in hot dimethylformamide and no satisfactory solvent was found. It gave the Griessmayer test and an orange solution in 2N-sodium hydroxide.

The overnight action of excess of ethereal diazomethane furnished the *octamethyl ether* which was washed with cold 2N-potassium hydroxide. It was almost insoluble in hot dimethylformamide, acetic anhydride, anisole, and acetophenone but crystallised from benzyl cyanide as pale cream-coloured needles, m. p. >365° (Found: C, 60·5; H, 3·85. $C_{36}H_{26}O_{16}$ requires C, 60·5; H, 3·75%).

Acetylation by 4 hours' refluxing with acetic anhydride and a little pyridine gave the sparingly soluble *octa-acetate* which separated from a large bulk of nitrobenzene, containing acetic anhydride, as colourless needles, m. p. 318—320° (Found: C, 57·3; H, 3·4. $C_{44}H_{34}O_{24}$ requires C, 56·8; H, 2·8%).

Synthesis of Flavogallol.—Copper bronze (6 g.) was added to a mixture of methyl 2-bromo-3 : 4 : 5-trimethoxybenzoate (10 g.) and dimethyl 5-bromo-2 : 3 : 4 : 2′ : 3′ : 4′-hexamethoxy-6 : 6′-diphenate (4 g.) at 220—230° (metal-bath) for 2 hr. After cooling, the mixture was triturated with chloroform and filtered and the filtrate washed successively with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated. Distillation afforded fractions: (*a*) b. p. 118—120°/0·1 mm. (1·4 g.), m. p. 81—82° (from aqueous methanol) undepressed by methyl tri-*O*-methylgallate; (*b*) b. p. 185—190°/0·03 mm. (4·1 g.), m. p. 109—110° (from aqueous methanol), undepressed by dimethyl hexamethoxydiphenate; and (*c*) b. p. 225—240°/0·015 mm. (1·8 g.), a viscous oil, hydrolysed by 2 hours' refluxing with potassium hydroxide (2 g.) in methanol (30 ml.). The resulting acid, isolated with ether, was a gum (halogen test negative) which afforded successive crops of crude hexamethoxydiphenic acid (0·23 g. in all) on slow evaporation of its aqueous-ethanolic solution. When the m. p. of these crystals had fallen to 215—225° no further crystalline material would separate. The filtrate was evaporated to dryness and the residue (1·4 g.) demethylated by 4 hours' refluxing with hydriodic acid (15 ml.; *d* 1·7) and acetic anhydride (5 ml.). An orange precipitate was rapidly formed. Dilution with water and centrifuging afforded a yellow powder which was washed with dilute sulphurous acid and water and dried in a desiccator (yield, 0·72 g.).

This phenol (0·72 g.) was refluxed with acetic anhydride (10 ml.) and pyridine (3 drops) for 3 hr., filtered hot, cooled, and poured into water (10 ml.). The precipitated *acetate* (0·55 g.) was collected and crystallised from acetic anhydride as colourless needles, m. p. 278—280° (decomp.)

undepressed by hexa-*O*-acetylflavogallol, m. p. 290—292° (Found : C, 55·8; H, 3·0%). This acetate was converted successively into flavogallol (negative Griessmayer test) and its *hexamethyl ether* which separated from dimethylformamide as yellow needles, m. p. 329—330° (Found : C, 60·3; H, 4·1%) undepressed by authentic hexa-*O*-methylflavogallol and showing an identical infrared adsorption spectrum.

The *hexabenzoate* had m. p. and mixed m. p. 326—328° (Found : C, 70·4; H, 3·6%).

3-2′-*Methoxybenzylcoumarin*.—β-*o*-Methoxyphenylpropionic acid (10 g.) and potassium hydrogen carbonate (5·27 g.) were dissolved in methanol, the solution evaporated to dryness, and the residue heated at 120° for 3 hr. The resulting potassium salt was heated with salicylaldehyde (7 g.) and acetic anhydride (15 ml.) at 170—180° for 18 hr. When cold, the mixture was stirred with water and extracted with ether. Washing the ether layer with potassium hydrogen carbonate solution removed a brownish acid (7·2 g.), purified *via* the methyl ester and identified as β-*o*-methoxyphenylpropionic acid. Evaporation of the ether then left a neutral fraction (8·8 g.) which was distilled giving fractions : (*a*) b. p. 140—150°/11 mm. (4·1 g.), crystallising from *cyclo*hexane as needles, m. p. 68—69° undepressed by coumarin ; and (*b*) b. p. 160—165°/0·01 mm. (3·2 g.), which crystallised from light petroleum (b. p. 60—80°) as colourless needles (2 g.) of 3-2′-*methoxybenzylcoumarin*, m. p. 95—96° (Found : C, 76·5; H, 5·4; OMe, 12·0. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3; OMe, 11·7%).

3-*o*-*Hydroxybenzylcoumarin* (XI).—The methyl ether (2 g.) was refluxed with hydriodic acid (5 ml. ; *d* 1·7) and acetic anhydride (5 ml.) for 3 hr. Dilution with water precipitated the *phenol* which crystallised from 50% ethanol as colourless needles (1·7 g.), m. p. 154—155° (Found : C, 76·1; H, 5·0. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·75%). Acetic anhydride and sodium acetate furnished the *phenylacetate*, crystallising in prisms (from *cyclo*hexane), m. p. 127—128° (Found : C, 73·5; H, 4·9. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

3-*o*-*Methoxyphenylcoumarin*.—*o*-Methoxyphenylacetic acid (10 g.) and potassium hydrogen carbonate (6·02 g.) were caused to react in methanol as before. The potassium salt, salicylaldehyde (7·4 g.), and acetic anhydride (15 ml.) were heated at 170—180° for 6 hr. On cooling, the mixture was stirred with water, taken up in chloroform, washed with potassium hydrogen carbonate solution, and dried (Na_2SO_4). Evaporation of the solvent left an oil which crystallised from acetic acid as needles (8·3 g.) of 3-*o*-*methoxyphenylcoumarin*, m. p. 139—140°. An analytical specimen separated from a large volume of ethanol as stout needles, m. p. 140—141° (Found : C, 76·1; H, 5·1. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·75%). Acidification of the carbonate extract precipitated a solid (1·5 g.), crystallising from 50% ethanol as colourless needles, m. p. 155—156°, probably the corresponding *O-acetylcoumaric acid* (Found : C, 69·7; H, 5·4. $C_{18}H_{14}O_5$ requires C, 69·3; H, 5·1%).

3-*o*-*Hydroxyphenylcoumarin* (XII).—Demethylation of the methyl ether as in the previous case afforded this *phenol* which separated from aqueous dioxan as colourless needles, m. p. 208—209° (Found : C, 75·0; H, 4·4. $C_{15}H_{10}O_3$ requires C, 75·6; H, 4·2%). The *phenylacetate* crystallised from 75% ethanol as colourless plates, m. p. 137—138° (Found : C, 72·3; H, 4·3. $C_{17}H_{12}O_4$ requires C, 71·8; H, 4·2%). Methylation of the phenol with diazomethane refurnished the methyl ether, m. p. and mixed m. p. 140—141°.

Neither 3-*o*-hydroxybenzylcoumarin nor 3-*o*-hydroxyphenylcoumarin reacted with hydrogen chloride or hydrogen bromide in benzene, acetic acid, ether, or dioxan with or without the addition of ferric chloride. Sulphuric acid reacted, to form water-soluble products from which the original coumarins could not be recovered.

Rufigallol (XIII ; R = R′ = H).—Anhydrous gallic acid (10 g.) was dissolved in 98% sulphuric acid (30 ml.) and heated on a water-bath for 2 hr., cooled, and poured into water. The resulting orange precipitate (2·1 g.) was centrifuged, dried, and acetylated by refluxing with acetic anhydride (25 ml.) and sulphuric acid (3 drops) for 2 hr. On cooling, the hexa-acetate, separated as yellow plates (1·6 g.) and, recrystallised from acetic anhydride, had m. p. 268—270° (decomp., in sealed evacuated tube; no m. p. previously recorded) (Found : C, 56·4; H, 4·0; Ac, 45·4. Calc. for $C_{26}H_{20}O_{14}$: C, 56·2; H, 3·6; 6Ac, 46·4%). For hydrolysis, the acetate (1 g.) was dissolved in boiling pyridine (20 ml.), and acetic acid (25 ml.) was added; a deep purple solution resulted. When concentrated hydrochloric acid (20 ml.) was added down the condenser, the mixture became orange and deposited rufigallol as a scarlet powder (0·6 g.) which was collected when cold. Good analytical figures were not obtained. Rufigallol was kept overnight with excess of ethereal diazomethane, the solvent evaporated, and the residue crystallised from ethyl acetate as orange-yellow needles of the tetramethyl ether (XIII ; R = Me, R′ = H), m. p. 251—252° (Found : C, 59·8; H, 4·8; OMe, 32·7. Calc. for $C_{18}H_{16}O_8$: C, 60·0; H, 4·5; OMe, 34·5%). Occasionally an unstable modification separated, having m. p.

239—240° (resolidifies and remelts at 251—252°). Klobukowski [6] records m. p. 235—237° for this substance.

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, May 31st,* 1956.]

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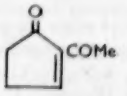
814. *Some Experiments with* cyclo*Pentanones.*

By R. M. ACHESON.

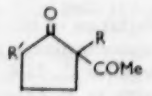
A number of unsuccessful attempts to prepare 2-acetyl*cyclo*pent-2-enone from 2-acetyl*cyclo*pentanone, 2-furylacetone, and 3-methyl*cyclo*hex-3-enone, and the preparation of these compounds, are described.

ALTHOUGH 2-acetyl*cyclo*-hexene and -pentene react with the sodium derivative of 6-methoxytetralone to yield tetracyclic compounds [1] these products have not proved valuable in the synthesis of steroids because methods of introducing substituents at position 17 are not yet available. The use of 5-monosubstituted 1-acetyl*cyclo*pentenes in this synthesis appears unpromising as the double bond is almost certain to migrate under the influence of the alkali, but this argument does not inevitably apply when the *cyclo*pentene has two substituents or a carbonyl group at position 5.

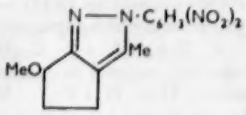
The unknown 2-acetyl*cyclo*pent-2-enone (I) was therefore the objective, and the first attempt was *via* 2-acetyl*cyclo*pentanone. This *cyclo*pentanone has been obtained from *cyclo*pentanone and ethyl acetate in the presence of sodium,[2] but the low yield (12%) and the necessity of purification through the copper salt was not encouraging. Replacement of the sodium by its hydride gave even less 2-acetyl*cyclo*pentanone with some di*cyclo*pentylidene*cyclo*pentanone, earlier obtained [3] from *cyclo*pentanone and sodium ethoxide. However cyclisation of ethyl 6-oxoheptanoate with sodium hydride gave the ketone (II) in satisfactory yield. 6-Oxoheptanoic acid, with a little glutaric acid, was more conveniently obtained from 2-methyl*cyclo*hexanone with aqueous potassium permanganate than by the use of other oxidants.[4]



(I)



(II) R = R' = H
(III) R = Br, R' = H
(IV) R = H, R' = Br



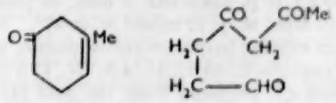
(V)

2-Acetyl*cyclo*pentanone reacted very readily with the theoretical quantity of bromine in aqueous potassium chlorate [5] but the resulting solution was very strongly acid and monobromination was incomplete. Better results were obtained in aqueous sodium acetate, the product after distillation being a colourless lachrymatory oil of the expected composition. The bromine probably initially attacks position 2, giving the derivative (III), but as the compound gave a sticky copper derivative and a deep red ferric chloride colour, rearrangement to the isomer (IV) or to 2-bromoacetyl*cyclo*pentanone had taken place.[6] Although the bromo-compound may be a mixture of all three isomers Kuhn–Röth determinations showed the presence of one *C*-Me group and therefore exclude the presence of

[1] Peak and Robinson, *J.*, 1937, 1581.
[2] Kuhn, Köhler, and Köhler, *Z. physiol. Chem.*, 1936, **242**, 171.
[3] Wallach, *Ber.*, 1896, **29**, 2955.
[4] Ruzicka, Seidel, Schinz, and Pfeiffer, *Helv. Chim. Acta*, 1948, **31**, 422; G.P. 812,073 (*Chem. Abs.*, 1953, **47**, 2769).
[5] Catch, Elliott, Hey, and Jones, *J.*, 1948, 272.
[6] Cf. Conrad, *Ber.*, 1896, **29**, 1042; Epprecht, *Annalen*, 1894, **278**, 69.

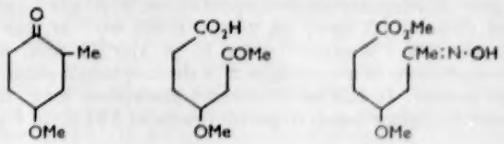
much 2-bromoacetyl*cyclo*pentanone unless a rearrangement took place under the conditions of oxidation. The compound is therefore probably largely the ketone (IV), but neither dehydrobromination with collidine or silver nitrate in pyridine, nor acid hydrolysis, gave identifiable products; 2-acetyl*cyclo*pentanone gave 6-oxoheptanoic acid with either dilute acid or alkali and no *cyclo*pentanone could be detected. The bromo-ketone (IV) with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid gave a yellow crystalline derivative containing one *C*-Me and one methoxyl group, and it did not lose methanol when heated alone. 2-Chloro-2-methyl*cyclo*hexanone similarly gives 2-methoxy-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone.[7] The *cyclo*pentanone derivative may be compound (V) or an isomer.

Alternative schemes based on the formation and cyclisation of the aldehyde (VII) were then examined. 3-Methyl*cyclo*hex-3-enone (VI), prepared in a comparatively high state of purity by a modification of Birch's method,[8] was ozonised at −80° in ethyl acetate and hydrogenated over palladised charcoal at −10°. Although the theoretical quantities of ozone and hydrogen were absorbed attempts to isolate the aldehyde (VII), or to cyclise it *in situ* to the ketone (I) by acid catalysis, gave only products of high molecular weight.



(VI) (VII) (VIII)

2-Acetonylfuran (VIII) was treated with acid, in the hope that it would yield the aldehyde (VII) which might simultaneously cyclise to the ketone (I): however it was either unaffected by aqueous or alcoholic sulphuric acid, or converted into black tars when the acid concentration was raised above ~30% or when heated. Tars were also obtained in attempts to prepare 2-acetonyl-2 : 5-dihydro-2 : 5-dimethoxyfuran from the ketone (VIII) with bromine in methanol.[9] 2-Acetonylfuran oxime formed an oily toluene-*p* sulphonate which also gave black tars when shaken with ethanol,[10] instead of the desired 1 : 1-diethoxyhept-2-ene-4 : 6-dione which it was proposed to reduce to the saturated acetal. Several attempts to prepare the last compound from acetone and ethyl γγ-diethoxybutyrate, obtained from the β-formylpropionate and ethyl orthoformate, also failed.



(IX) (X) (XI)

As 2-methyl*cyclo*hexanone was so easily oxidised to 6-oxoheptanoic acid it was hoped that the 4-methoxy-derivative (IX) would similarly yield 4-methoxy-6-oxoheptanoic acid (X) which after esterification might undergo Dieckmann condensation followed by loss of methanol, leading to 2-acetyl*cyclo*pent-2-enone (I). 4-Methoxy-2-methylphenol was obtained from *p*-methoxyphenol by treatment with formaldehyde and dimethylamine, followed by hydrogenation over Raney nickel, a much more convenient catalyst than the copper chromite previously used.[11] Further hydrogenation, after removal of all traces of amine which prevented reaction, yielded the *cyclo*hexanol, which was oxidised to the *cyclo*hexanone (IX) with chromic acid. Unfortunately attempts to oxidise this ketone to the acid (X) with potassium permanganate failed and the ether linkage appeared to be

[7] Warnhoff and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 494.
[8] Birch, *J.*, 1946, 593.
[9] Cf. Clauson-Kaas, Limborg, and Fakstorp, *Acta Chem. Scand.*, 1948, **2**, 109.
[10] Cf. Vargha, Ramonczai, and Bite, *J. Amer. Chem. Soc.*, 1948, **70**, 371.
[11] Reeve and Sadle, *ibid.*, 1950, **72**, 3252.

attacked. An alternative method [12] of ring opening with ethyl nitrite and sodium ethoxide gave ethyl 6-hydroxyimino-4-methoxyheptanoate (XI) in poor yield; hydrolysis with oxalic acid gave no ketonic product, while boiling with dilute alkali followed by treatment with 2 : 4-dinitrophenylhydrazone gave the derivative from β-formylpropionic acid.

*cyclo*Pentane-1 : 2-dione has been obtained from *cyclo*pentanone by bromination, hydrolysis to 2-hydroxy*cyclo*pentanone, and oxidation with ferric chloride without isolation of the intermediates. With 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid it gave the hydrazone of 2-methoxy*cyclo*pent-2-enone, while with excess of aqueous or alcoholic reagent the normal bis-derivative was formed. 2-Methoxy*cyclo*pent-2-enone was obtained from the diketone with diazomethane.

Experimental

6-Oxoheptanoic Acid.—After 2-methyl*cyclo*hexanone (45 g.) had been stirred with potassium permanganate (108 g.) and water (3·6 l.) for about 12 hr. at room temperature almost no permanganate remained. The mixture was clarified with sulphur dioxide, acidified with concentrated sulphuric acid (22 ml.), and continuously extracted with ether (24 hr.). Distillation of the dried extract gave 6-oxoheptanoic acid (39 g.), b. p. 158—162°/9 mm., as plates, m. p. 33—34°, and glutaric acid (2·4 g.), b. p. 185—190°/9 mm., m. p. or mixed m. p. 97°. *6-Oxoheptanoic acid 2 : 4-dinitrophenylhydrazone* separated from ethanol in orange-yellow prisms, m. p. 144° (Found: C, 48·1; H, 4·8; N, 17·7. $C_{13}H_{16}O_6N_4$ requires C, 48·1; H, 4·9; N, 17·3%). Methyl 6-oxoheptanoate, b. p. 108—112°/13 mm. (35·9 g.), prepared from the acid (41·2 g.) by 4 hours' refluxing with methanol (50 ml.) and concentrated sulphuric acid (3 ml.), gave a *2 : 4-dinitrophenylhydrazone*, yellow needles (from methanol), m. p. 123—124° (Found: C, 49·7; H, 5·6. $C_{14}H_{18}O_6N_4$ requires C, 49·7; H, 5·3%).

*2-Acetyl*cyclo*pentanone* (II).—(i) Sodium hydride (9·6 g.) was added to a mixture of ethyl 6-oxoheptanoate (7·2 g.) in ether (50 ml.) under nitrogen and reaction started by the addition of a drop of ethanol and warming; more ester (10 g.) in ether was then added and the reaction completed according to Swamer and Hauser's procedure.[13] Sodium ethoxide has also [14] been used for the cyclisation. 2-Acetyl*cyclo*pentanone (10 g.), isolated by ether, had b. p. 82—86°/12 mm., n_D^{17} 1·4920, and gave a deep violet ferric chloride colour in ethanol.

(ii) Sodium hydride (9·6 g.) reacted with ethyl acetate (35·2 g.) and *cyclo*pentanone (24·8 g.) under Swamer and Hauser's conditions.[13] Distillation of the product, purified by its copper salt, gave 2-acetyl*cyclo*pentanone (2·3 g.), n_D^{18} 1·4917, b. p. 75—80°/11 mm., and a pale yellow unidentified oil (4·9 g.), b. p. 162—164°/12 mm. Distillation of the product which did not form a copper salt gave di*cyclo*pentylidene*cyclo*pentanone, b. p. 194—198°/11 mm., as yellow needles, m. p. 84—85° (Found: C, 83·0; H, 9·3%; *C*-Me, 0·0; *M*, 243. Calc. for $C_{15}H_{20}O$: C, 83·2; H, 9·3%; *M*, 216). Wallach [3] gives b. p. 190°/12 mm. and m. p. 76—77°. It did not form a semicarbazone or a crystalline 2 : 4-dinitrophenylhydrazone, and Wallach was unable to prepare an oxime. It had an ultraviolet absorption max. in EtOH at 3000 Å (ε 15,300), and infrared absorption bands in paraffin paste at 5·91 (CO), 6·17, and 6·22 μ with an inflexion at 6·08 μ.

2-Acetyl*cyclo*pentanone was very slowly hydrolysed by cold 10% aqueous potassium hydroxide, but boiling 20% aqueous potash (2½ hr.) [15] or aqueous 4N-sulphuric acid gave 6-oxoheptanoic acid (80%), m. p. or mixed m. p. 35°. No *cyclo*pentanone could be detected.

The mixture of red and yellow crystals obtained when 2-acetyl*cyclo*pentanone (0·3 g.), 2 : 4-dinitrophenylhydrazine (0·5 g.), methanol (25 ml.), and sulphuric acid (0·5 ml., *d* 1·84) were left at room temperature for 16 hr. was separated as the red material (0·05 g.) did not dissolve in boiling methanol (15 ml.). The red material, probably *2-acetyl*cyclo*pentanone bis-2 : 4-dinitrophenylhydrazone* was obtained as red-brown prisms, m. p. 219° (decomp.), by dissolution in a large volume of boiling ethyl acetate followed by almost complete evaporation (Found: C, 47·6; H, 4·1; N, 23·4. $C_{19}H_{18}O_8N_8$ requires C, 46·9; H, 3·7; N, 23·0%). The methanol-soluble *2-(2 : 4-dinitrophenyl)-3-methyl*cyclo*penta*[c]*pyrazole* or an isomer), formed from one of the two monodinitrophenylhydrazones possible on cyclodehydration, separated from this solvent in yellow prisms, m. p. 165° (Found: C, 54·1; H, 4·2; N, 19·2. $C_{13}H_{12}O_4N_4$ requires C, 54·2; H, 4·2; N, 19·4%).

[12] Woodward and Doering, *J. Amer. Chem. Soc.*, 1945, **67**, 860.
[13] Swamer and Hauser, *ibid.*, 1950, **72**, 1352.
[14] Blaise and Köhler, *Bull. Soc. chim. France*, 1910, **7**, 710.
[15] Cf. Hauser, Swamer, and Ringler, *J. Amer. Chem. Soc.*, 1948, **70**, 4023.

Bromination of 2-Acetylcyclopentanone.—Bromine (0·64 g.) was added with shaking to a mixture of the ketone (1·5 g.), water (10·0 ml.), and sodium acetate (5·0 g.) at room temperature; the colour disappeared very quickly. The oily product was collected with ether, washed with (2—3%) aqueous sodium hydrogen carbonate and water, dried, and immediately distilled, to give bromo-2-acetylcyclopentanone as a colourless lachrymatory oil, b. p. 75—77°/0·2 mm. (1·8 g.), n_D^{17} 1·553 (Found: C, 40·9; H, 4·4; Br, 39·2; *C*-Me, 5·5. Calc. for $C_7H_9O_2Br$: C, 41·0; H, 4·4; Br, 39·0; 1*C*-Me, 7·3%). It decomposed if distillation was attempted at 10 mm., gave a deep red ferric chloride colour in ethanol and a sticky green copper salt, and decomposed to a black tar in a few hours at room temperature.

The deep red solution obtained on mixing the bromo-ketone (1·0 g.), 2 : 4-dinitrophenylhydrazine (3·0 g.), methanol (50 ml.), and concentrated sulphuric acid (5 ml.) deposited a dark red solid (1·0 g.) at room temperature in 18 hr. After crystallisation from ethyl acetate this solid gave 2-(2 : 4-*dinitrophenyl*)-6-*methoxy*-3-*methyl*cyclo*penta*[c]*pyrazole* (V, or an isomer), separating from ethanol in yellow needles, m. p. 147° (Found: C, 52·8, 52·9; H, 4·2, 4·5; N, 17·8; Br, 0·0; OMe, 10·0, 10·7; *C*-Me, 6·0. $C_{14}H_{14}O_5N_4$ requires C, 52·8; H, 4·4; N, 17·6; 1OMe, 9·7; 1*C*-Me, 4·7%). No other crystalline material could be obtained from the mother-liquors.

3-*Methyl*cyclo*hex*-3-*enone* (VI).—2 : 5-Dihydro-3-methylanisole [8] (20·5 g.) was shaken with saturated aqueous sodium hydrogen sulphite, saturated with sulphur dioxide, at 0°. After 12 hr. the precipitate (41 g.) was collected, washed with methanol and ether, and decomposed with potassium carbonate (40 g.) in water (120 ml.). Evaporation of the dried ether extracts gave largely 3-methyl*cyclo*hex-3-enone (7·8 g.), b. p. 61—62°/14 mm., $\lambda_{max.}$ 2310 (ε 1800 in methanol) (cf. Birch [8]). The ultraviolet absorption was unchanged after the material had remained at room temperature for 3 weeks in a Pyrex flask. The *semicarbazone*, prepared in the cold, was washed with aqueous potassium carbonate and dried before crystallisation, and separated from ethyl acetate in long thin plates, m. p. 157—158° (Found: C, 57·3; H, 7·5; N, 24·8. $C_8H_{13}ON_3$ requires C, 57·5; H, 7·8; N, 25·2%). Birch [8] gives m. p. 159—161° but no analysis or ultraviolet data. The ultraviolet absorption spectrum in methanol showed $\lambda_{max.}$ 2280 (ε 13,000).

Methyl αβ-*Epoxy*-β-2-*furyl*-x-*methylpropionate.*—A dry methanol (75 ml.) solution of sodium (6·9 ml.) was added during 3 hr. to a vigorously stirred mixture of methyl α-chloropropionate (37·6 g.), furfuraldehyde (20·0 g.), and methanol (25 ml.) at 0°. After 12 hours' stirring at 20° the methanol was removed *in vacuo* at this temperature and the residue treated successively with ether (150 ml.) and aqueous N-hydrochloric acid (110 ml.) at 0°. The ether extracts were dried, washed with aqueous sodium hydrogen carbonate, and evaporated, giving the required ester (23·9 g.), b. p. 116—221°/11 mm. Wolff [16] gives b. p. 112—116°/9 mm.

2-*Acetonylfuran* (VIII).—The above ester (13·3 g.) dissolved in 2 min. when shaken with a cold solution of sodium hydroxide (3·5 g.) in water (20 ml.) and methanol (5 ml.), and after 5 min. aqueous 7N-sulphuric acid (26 ml.) was added. Much carbon dioxide was evolved. Ether extracts were washed with aqueous sodium hydrogen carbonate, dried, and evaporated, giving 2-acetonylfuran (4·0 g.), smelling of horse-radish, b. p. 70—72°/13 mm. (Found: C, 68·0; H, 6·6. $C_7H_8O_2$ requires C, 67·7; H, 6·5%). Darzens [17] gives b. p. 179—180° but no analysis. The *semicarbazone* separated from ethanol in prisms, m. p. 173—174° (Found: C, 53·0; H, 6·2; N, 23·5. $C_8H_{11}O_2N_3$ requires C, 53·0; H, 6·1; N, 23·2%). Darzens [17] gives m. p. 173—174° but no analysis. The *oxime* was a liquid, b. p. 110°/8 mm. (Found: C, 60·4; H, 6·5; N, 10·2. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%). A crystalline 2 : 4-dinitrophenylhydrazone was not formed in methanolic sulphuric acid.

2-*Hydroxy*-5-*methoxy*-NN-*dimethylbenzylamine.*—40% Aqueous formaldehyde (23 g.) was added during 80 min. to *p*-methoxyphenol (30 g.) in 35% aqueous dimethylamine (110 g.) with stirring below 25°. After 1 hr. at room temperature the mixture was heated on a steam-bath for 4 hr. Two layers were formed. The lower layer, and a benzene extract of the aqueous layer, were washed with water, dried, and distilled, giving the phenol (33 g.), b. p. 114—122°/1 mm., as yellow prisms, m. p. 47° (lit.,[11] m. p. 50—51°).

4-*Methoxy*-2-*methylphenol.*—The foregoing amine (58 g.) in ethanol (45 ml.) was hydrogenated over Raney nickel at 180—200°/100 atm. Reduction was complete in 2 hr. and the crude product obtained on evaporation of the filtered ethanol solution was washed in ether with 2N-sulphuric acid, dried, and distilled as an almost colourless oil (38 g.), b. p. 132—138°/15 mm., m. p. 70° (lit.,[11] 70·5°).

[16] Wolff, G.P. 702,007 (*Chem. Abs.*, 1942, **36**, 95).
[17] Darzens, *Compt. rend.*, 1906, **142**, 215.

4-*Methoxy*-2-*methyl*cyclo*hexanol*.—4-Methoxy-2-methylphenol (25 g.) was hydrogenated at 160—170°/120 atm. over Raney nickel in the presence of a trace of ethanol. Reduction was complete in 1 hr., and the *cyclo*hexanol (22·1 g.), collected with ether, distilled as a peppermint-smelling oil, b. p. 102—106°/13 mm., n_D^{17} 1·4692 (Found : C, 66·6; H, 11·3; OMe, 21·9. $C_8H_{16}O_2$ requires C, 66·7; H, 11·1; OMe, 21·5%). Its *p-nitrobenzoate*, prepared in pyridine, separated from ethanol in prisms, m. p. 127° (Found : C, 61·3; H, 6·7. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·5%). On one occasion when the temperature reached 190° during the reduction about one-third of the product was hexahydro-*o*-cresol, b. p. 70—74°/11 mm., n_D^{18} 1·4649 (Found : C, 73·5; H, 12·2. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%), whose infrared absorption spectrum was identical with that of an authentic specimen.

4-*Methoxy*-2-*methyl*cyclo*hexanone* (IX).—Sodium dichromate dihydrate (20·2 g.) in water (30 ml.) and sulphuric acid (8 ml.) was added, with vigorous stirring, in 10—15 min. to a mixture of 4-methoxy-2-methyl*cyclo*hexanol (24 g.), water (130 ml.), and concentrated sulphuric acid (18 ml.). An exothermic reaction took place and the mixture was kept at 45° for a total of 30 min. The cyclo*hexanone* separated as the upper layer, and after the addition of methanol (3 ml.) to destroy excess of dichromate, it was collected in ether, washed with aqueous potassium hydrogen carbonate, and dried. Distillation gave an oil (16·7 g.), b. p. 92—97°/15 mm. (Found : C, 67·8; H, 10·2. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in yellow needles, m. p. 138° (Found : C, 52·2; H, 5·9; N, 17·4. $C_{14}H_{18}O_5N_4$ requires C, 52·2; H, 5·6; N, 17·4%).

Ethyl 6-*Hydroxyimino*-4-*methoxyheptanoate*.—4-Methoxy-2-methyl*cyclo*hexanone (6·16 g.), followed by freshly dried and distilled ethyl nitrite (4·0 ml.), was added to a solution of sodium (1·0 g.) in dry ethanol (150 ml.) at 0°. After 18 hr. at this temperature, carbon dioxide was passed through the solution at room temperature to neutrality. The dark solution was treated with charcoal, filtered, and evaporated, and the dark residue distilled. The *oxime* (2·2 g.) was obtained as a pale yellow oil, n_D^{20} 1·4646, b. p. 164—170°/7 mm., 115°/0·07 mm. (Found : C, 55·0; H, 8·8; N, 6·4; OMe + OEt, 31·8. $C_{10}H_{19}O_4N$ requires C, 55·3; H, 8·8; N, 6·5; 1OMe + 1OEt, 35·0%). Unless great care is taken at the beginning of the distillation the dark residue undergoes a vigorous decomposition to a black froth, from which it is possible to isolate very little of the desired product.

The hydroxyimino-ester (0·7 g.) was refluxed for 30 min. with aqueous 2N-sodium hydroxide (20 ml.), and the solution acidified and extracted with ether. Evaporation of the extract gave an oil which with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid gave a yellow precipitate, identical with that obtained on treating the extracted aqueous solution with this reagent. Recrystallisation of the precipitate from aqueous acetic acid gave γ-(2 : 4-dinitrophenylhydrazono)butyric acid as yellow prisms (Found : C, 42·6; H, 3·6; N, 19·4. Calc. for $C_{10}H_{10}O_6N_4$: C, 42·6; H, 3·5; N, 19·9%), m. p. and mixed m. p. 199—200°; the infrared absorption spectra of this and an authentic specimen were also identical.

Ethyl γγ-*Diethoxybutyrate*.—Ethyl β-formylpropionate (35·3 g.), ethanol (47 ml.), ethyl orthoformate (45 g.), and ammonium chloride (0·75 g.) were refluxed for 70 min., ethanol and ethyl formate were removed, and the residue was cooled, diluted with ether (100 ml.), and treated with ice-water (20 ml.). Evaporation of the dried ether extracts gave the acetal (49·1 g.), b. p. 111—116°/16 mm., n_D^{20} 1·4180 (Found : C, 58·5; H, 9·8. Calc. for $C_{10}H_{20}O_4$: C, 58·8; H, 9·8%) (lit.,[18] b. p. 101—102°/12 mm.).

Ethyl β-formylpropionate with 2 : 4-dinitrophenylhydrazine in aqueous 2N-hydrochloric acid gave the *hydrazone*, which separated from ethanol as yellow needles, m. p. 200° (Found : C, 42·6; H, 3·6; N, 19·4. $C_{10}H_{10}O_6N_4$ requires C, 42·6; H, 3·5; N, 19·9%).

cyclo*Pentane*-1 : 2-*dione*.—A mixture of *cyclo*pentanone (60 ml.), acetic acid (31 ml.), and water (135 ml.) was vigorously stirred and a few drops of bromine were added. The whole was then heated at *ca.* 70° until the colour disappeared, to start the reaction. The remaining bromine (total 38·5 ml.) was then added during 15 min. with stirring, the temperature being kept at 55—60° by external cooling. If the temperature is allowed to exceed 60° for an appreciable time an inferior yield of a less pure product is obtained.[19] The stirred mixture was then neutralised (Congo-red) with solid sodium carbonate, and the pale yellow bromo*cyclo*pentanone (93 g.), which separated below the aqueous layer, was washed twice with water.

This crude bromo-ketone (127·5 g.) was stirred vigorously (important) with water (830 ml.) at 95—98° until dissolution was complete (10 min.).[20] Then ferric chloride (200 g. ; anhydrous)

[18] Carrière, *Ann. Chim.*, 1922, **17**, 70.
[19] Cf. Kötz, Blendermann, Kárpáti, and Rosenbusch, *Annalen*, 1913, **400**, 51.
[20] Cf. Inhoffen, *Chem. Ber.*, 1954, 491.

in hot water (250 ml.) was added during 5 min. with vigorous stirring. After a few more minutes at 95—98° the mixture was cooled to *ca.* 40°, saturated with ammonium sulphate, and continuously extracted with ether. Distillation of the dried extract gave *cyclo*pentane-1 : 2-dione (30·7—33·0 g.), b. p. 78—86°/8 mm., yellow prisms, m. p. 55—56° (lit.,[20] m. p. 55—56° for a product from 2-chloro*cyclo*pentanone). The diketone with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid gave *2-methoxycyclopent-2-enone* 2 : 4-*dinitrophenylhydrazone*, which separated from ethyl acetate in orange-red prisms, m. p. 207—208° (slight decomp.) (Found : C, 48·8; H, 4·2; N, 20·0; OMe, 8·1. $C_{12}H_{12}O_5N_4$ requires C, 49·3; H, 4·1; N, 19·2; OMe, 10·6%). Use of an excess of the reagent, or of water as solvent, leads to the *bis*-2 : 4-*dinitrophenylhydrazone*, orange-red prisms (from acetic acid), m. p. 250—252° (decomp.) (Found : C, 44·6; H, 3·1; N, 24·2. $C_{17}H_{14}O_8N_8$ requires C, 44·5; H, 3·1; N, 24·5%).

2-Methoxycyclopent-2-enone.—When diazomethane (9·7 g.) in ether (570 ml.) was added to *cyclo*pentane-1 : 2-dione (21·5 g.) in ether (83 ml.) a vigorous reaction took place. After about 1 hr. the mixture was distilled, giving *2-methoxycyclopent-2-enone* (17·2 g.), n_D^{20} 1·4980 b. p. 112—114°/16 mm. (Found : C, 64·5; H, 7·1. $C_6H_8O_2$ requires C, 64·3; H, 7·1%).

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815. *Some Degradation Products of Fumagillin.*

By JUSTUS K. LANDQUIST.

Fumagillin is a half ester of octatetraene-1 : 8-dicarboxylic acid with an alcohol, $C_{16}H_{26}O_4$, which contains an epoxide ring and two other rings, one of which contains oxygen. One carbon atom of the epoxide ring carries a 3-methylbut-2-enyl group while the other is probably part of a *cyclo*hexane ring. Ozonolysis effects the step-wise removal of these groups and subsequent reduction yields alcohols containing ten and eleven carbon atoms. The ring system in these alcohols has not been identified, but their behaviour with oxidising agents excludes some possible structures.

THE discovery of fumagillin followed observations of its activity against bacteriophage.[1, 2] Fumagillin has had only moderate success as a drug for the treatment of amœbiasis, but its outstanding activity against *Entamoeba histolytica in vitro*, and its other biological properties make the elucidation of its structure a matter of particular interest. It has been shown [3, 4] to be a half ester of octa-1 : 3 : 5 : 7-tetraene-1 : 8-dicarboxylic acid, but further progress has been hindered by the instability of fumagillin [5] and its derivatives, and by the considerable difficulty of obtaining crystalline, or even homogeneous, degradation products.[6, 7]

Fumagillin is rapidly hydrolysed by cold 0·1N-sodium hydroxide solution, giving octa-1 : 3 : 5 : 7-tetraene-1 : 8-dicarboxylic acid and an alcohol, $C_{16}H_{26}O_4$, for which the name "fumagillol" is proposed. This alcohol was first obtained as a syrup which crystallised only slowly after purification by counter-current distribution between *n*-hexane and water (the observed distribution was close to that calculated for a pure substance), but later preparations crystallised without difficulty. The infrared spectra of syrupy, crystalline, and distilled samples were identical. Schenck [6] and Tarbell [7] and their collaborators employed more drastic conditions of hydrolysis and obtained only a syrup which they called "alcohol I." Fumagillol contains one methoxyl group, two *C*-methyl

[1] Eble and Hanson, *Antibiotics and Chemotherapy*, 1951, **1**, 54.
[2] Asheshov, Strelitz, and Hall, *ibid.*, 1952, **2**, 361.
[3] Schenck, Hargie, Tarbell, and Hoffman, *J. Amer. Chem. Soc.*, 1953, **75**, 2274.
[4] Brown and Landquist, *Chem. and Ind.*, 1953, 973.
[5] Garrett, and Eble, *J. Amer. Pharm. Assoc.*, 1954, **43**, 385; Eble and Garrett, *ibid.*, p. 536; Garrett, *ibid.*, p. 539.
[6] Schenck, Hargie, and Isarasena, *J. Amer. Chem. Soc.*, 1955, **77**, 5606.
[7] Tarbell, Hoffman, Al-Kazimi, Page, Ross, Vogt, and Wargotz, *ibid.*, p. 5610.

groups, one active hydrogen atom, and no carbonyl group. Hydrogenation indicates that there is one double bond; infrared data (bands at 830 and 1673 cm.$^{-1}$ absent in dihydrofumagillol), and the ultraviolet absorption spectrum of the tetranitromethane adduct [8] show this to be doubly or triply substituted.

The nature of the hydroxyl group is uncertain, but the ease of hydrolysis of fumagillin and the failure of fumagillol to give characterisable esters or similar functional derivatives suggest that it is tertiary. The infrared spectrum shows strong absorption at 1095 cm.$^{-1}$ which might be attributable to an acyclic secondary alcohol, to a cyclic tertiary alcohol, or to the methoxyl group. The hydroxyl stretching frequency (3571 cm.$^{-1}$) in dilute carbon tetrachloride solution suggests that intramolecular hydrogen bonding occurs. An attempted Oppenauer oxidation gave a syrup which showed only faint carbonyl absorption; a secondary alcohol should have given a more definite result. Tarbell *et al.*[7] obtained a ketone, $C_{16}H_{24}O_4$, by oxidation of " alcohol I " with chromium trioxide in pyridine, but their product contained a hydroxyl group. The formation of this must have involved fission of a cyclic ether link, and the carbonyl group might have originated from oxidation at this point and not from the original hydroxyl group.

Fumagillol reacts rapidly with cold dilute (0·1N) hydrochloric acid, giving a chlorohydrin, probably $C_{16}H_{27}O_4Cl$, containing two active hydrogen atoms. It rapidly liberates one equivalent of alkali from sodium thiosulphate solution, giving a product which on alkaline hydrolysis yields a disulphide, $C_{32}H_{54}O_8S_2$. These reactions suggest the presence of an epoxide ring, since cyclic ethers with larger rings react slowly or not at all, and addition of hydrogen chloride at the double bond would not produce an additional active hydrogen atom. The reaction with thiosulphate is also given by dihydrofumagillol. The formation of a carbonyl compound (with loss of reactivity to thiosulphate) when fumagillol is boiled with magnesium bromide in butyl ether, and the loss of reactivity to thiosulphate on reduction with lithium aluminium hydride or on acid or alkaline hydrolysis, are further indications that an epoxide group is present. Alkaline hydrolysis of fumagillin in methanol affords a syrupy alcohol with twice the methoxyl content of fumagillol, presumably through addition of methanol at the epoxide group. Tarbell *et al.*[7] found that hydration occurs on treatment of " alcohol I " with aqueous sodium hydroxide, and hydration or addition of ethanol during the acid hydrolysis of fumagillin. The compound $C_{23}H_{31}O_9N_2Cl$ obtained from dihydrofumagillol and 3 : 5-dinitrobenzoyl chloride [6] is presumably formed by the addition of the acid chloride or hydrogen chloride to the epoxide group, but the presence of two active hydrogen atoms in this compound is not readily explained. It has not been possible to demonstrate a reaction between sodium thiosulphate and fumagillin or its methyl ester, possibly because of interference by the carboxyl or ester group, but it is unlikely that the epoxide group is formed during the hydrolysis of fumagillin, particularly as this would require a free hydroxyl group, *i.e.*, a second active hydrogen atom, in the fumagillin molecule. It is significant that a strain of *Aspergillus fumigatus* other than the ones producing fumagillin has been shown to produce epoxysuccinic acid.[9]

Hydrolysis of the epoxide ring in fumagillol proceeds slowly in alkaline solution, but more rapidly in dilute sulphuric acid, giving syrups with complex infrared spectra devoid of carbonyl bands. The product obtained with cold dilute sulphuric acid appeared to be the most homogeneous, and on oxidation with periodate it consumed 0·75—1·5 mols. in neutral solution and 1·5—2·3 mols. in acid solution. Among the oxidation products were acetone and a volatile C_6 carbonyl compound which were isolated as their 2 : 4-dinitrophenylhydrazones. The non-volatile oxidation product was an intractable syrup which decomposed on attempted distillation in a high vacuum. From the behaviour of fumagillol on ozonolysis, it appears likely that the C_6 carbonyl compound is 4-methylpent-3-enal, but attempts to confirm this by synthesis of the aldehyde from 4-methylpent-3-enoic acid were unsuccessful: distillation of the calcium salt with calcium formate gave only small amounts of carbonyl compounds, of which only acetaldehyde was identified, and the main product appeared to be a lactone (infrared absorption at 1778 and 1763 cm.$^{-1}$); reduction of the *N*-methylanilide with lithium aluminium hydride gave a complex mixture; and treatment

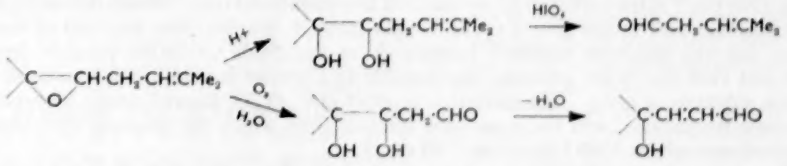
[8] Heilbronner, *Helv. Chim. Acta*, 1953, **36**, 1121.
[9] Birkinshaw, Bracken, and Raistrick, *Biochem. J.*, 1945, **39**, 70.

of the ethylthio-ester with Raney nickel gave 4-methylpent-2-enal; ethyl 4-methylpent-3-enoate when treated with sodium gave an impure acyloin which polymerised on distillation, and oxidation of the supposed acyloin or the corresponding glycol with periodate gave several products of which only acetone and 3-methylbut-2-enal could be characterised.

Ozonolysis of fumagillol in ethyl acetate followed by hydrogenation over palladium–calcium carbonate gave two crystalline products, an aldehyde, $C_{13}H_{20}O_5$,[6] and an acid, $C_{13}H_{20}O_6$, together with acetone [6] and much amorphous material probably arising from further degradation of the molecule. The ordinary conditions of ozonolysis involving prolonged treatment with ozonised oxygen may well lead to general oxidative degradation of an unstable molecule, but treatment of fumagillol with a solution of ozone (1 equivalent) in ethyl acetate did not give a better yield of aldehyde. The aldehydic ozonolysis product was shown to be αβ-unsaturated by its ultraviolet and infrared spectra, and like crotonaldehyde it liberated alkali slowly from sodium thiosulphate solution. It did not give a chlorohydrin with dilute hydrochloric acid. It was unstable to chromatography on alumina, and on oxidation with neutral or acid permanganate it consumed 4·5—5 atoms of oxygen. The C_{13} acid is presumably the one derived from the aldehyde by oxidation without other change of structure, but this has not been proved, and the infrared carbonyl frequency (1715 cm.$^{-1}$) is high for an αβ-unsaturated acid.

Ozonolysis of the C_{13} aldehyde under the conditions used for fumagillol gave a mixture which was partially separable by chromatography on silica, the main fraction being a weakly lævorotatory syrup. Methylglyoxal was also formed, and was identified by the melting point and ultraviolet absorption of its bis-2 : 4-dinitrophenylhydrazone; the infrared spectrum and *X*-ray powder photograph, however, showed small differences from those of authentic methylglyoxal bis-2 : 4-dinitrophenylhydrazone which could be attributed to the presence of a small amount of glyoxal bis-2 : 4-dinitrophenylhydrazone (Schenck *et al.*[6] obtained glyoxal on ozonolysis of the C_{13} aldehyde).

The splitting-off of a C_6 fragment by periodate oxidation after hydrolysis of the epoxide group shows that there are five carbon atoms attached to one side of the epoxide ring and not joined to the rest of the molecule in a cyclic structure (the formation of acetone in this experiment must be attributed to a side reaction). The formation of the αβ-unsaturated C_{13} aldehyde on ozonolysis involves the destruction of the epoxide group which must be so placed that it generates the new double bond. These results can be interpreted by the annexed scheme.

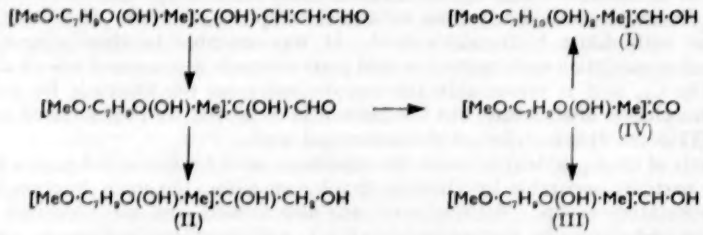


The formation of γ-methylvaleric acid in the oxidation of tetrahydrofumagillol [7] and the isolation of ethyl *iso*pentyl ketone on the dehydrogenation of hexahydrofumagillol [6] support this partial structure. The formation of methylglyoxal in the ozonolysis of the C_{13} aldehyde is an anomaly, but a C_{11} fragment can be isolated from this ozonolysis (see below) and on the present intepretation the methylglyoxal must arise from the disruption of some other part of the molecule. It may indicate that the methyl and the hydroxyl group are attached to the same carbon atom. The C_{13} aldehyde has a strong infrared band at approx. 980 cm.$^{-1}$, characteristic of a *trans*-disubstituted ethylene.

The part of the molecule not accounted for must be a saturated bicyclic structure, $C_9H_{16}O_3$, containing the hydroxyl and the methoxyl group, a *C*-methyl group, and the other oxygen atom, and unless the rings are small one of them must include a carbon atom of the epoxide group. Ozonolysis of the C_{13} aldehyde should give compounds with a carbonyl group directly attached to or incorporated in the fundamental ring system at the position of the original epoxide group.

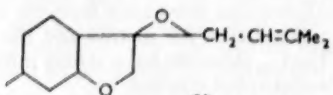
Reduction of the weakly lævorotatory ozonolysis product from the C_{13} aldehyde with

lithium aluminium hydride gave two crystalline alcohols, $C_{11}H_{20}O_5$ and $C_{10}H_{20}O_4$. These could not be obtained by similar reduction of the other fractions from the ozonolysis, of the permanganate oxidation product of the C_{13} aldehyde, of the periodate oxidation product of fumagillol, or of a substance obtained by oxidising the C_{13} acid with hydrogen peroxide–osmium tetroxide and then with periodate. A fraction from the ozonolysis of fumagillol which appeared (from infrared spectroscopy) to consist largely of a mixture of C_{13} aldehyde and C_{13} acid was ozonised and reduced with lithium aluminium hydride, giving another crystalline alcohol, $C_{10}H_{18}O_4$. The isolation of the C_{10} alcohols indicates that a formyl group has been lost during ozonolysis; similar reactions, for example, the formation of phenols during ozonolysis of some cinnamic esters,[10] have been reported. The simplest interpretation of these reactions is shown by the scheme below.

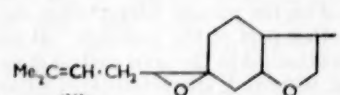


The formation of a compound $C_{10}H_{20}O_4$ must also involve the reductive fission of the remaining oxygen bridge; instances are known where lithium aluminium hydride splits a tetrahydrofuran ring, although more vigorous reaction conditions are usually needed. The *C*-methyl content of this alcohol indicates that no new methyl group has been generated unless it is in an *iso*propyl group. When the C_{10} and C_{11} alcohols were treated with periodic acid the compound $C_{10}H_{18}O_4$ consumed 0·15 mol. in three days and the others did not react. This unexpected result indicates that $C_{10}H_{20}O_4$ (I) cannot be a 1 : 2-glycol, which would be formed if the side chain is β to the oxygen bridge; and $C_{11}H_{20}O_5$ cannot be (II), but must be an isomer formed by migration of the nuclear hydroxyl group. The alcohol $C_{10}H_{18}O_4$ (III) was oxidised with chromic acid to a cyclic ketone, probably (IV). The crude product showed a single infrared carbonyl frequency at 1714 cm.$^{-1}$; this would have been displaced to *ca.* 1740 cm.$^{-1}$ if the carbonyl group was in a five-membered ring. Oxidation of $C_{11}H_{20}O_5$ with chromic acid might give a cyclic ketone through the complete removal of the side chain, but the observed carbonyl frequencies of the crude oxidation product (approx. 1706 and 1738 cm.$^{-1}$) are probably attributable to a ketone (not in a five-membered ring) and an aldehyde or ester. The oxidation product of $C_{10}H_{20}O_4$ showed strong absorption at the same frequencies, and the ozonolysis fraction from which the alcohols were obtained absorbed strongly at 1700 but not at 1740 cm.$^{-1}$.

From the selenium dehydrogenation of tetrahydrofumagillol Tarbell *et al.*[7] isolated a substance with chemical and physical properties resembling those of a benzofuran, and this suggests that the fundamental ring system is a furano*cyclo*hexane. In view of the formula of fumagillol, $C_{15}H_{23}O_5{\cdot}OMe$, and the known structure of the side-chain, $Me_2C{:}CH{\cdot}CH_2$,



(V)



(VI)

it might well be related to the terpenes, and on this hypothesis partial formulæ such as (V) and (VI) deserve consideration. The data from the oxidation of the C_{10} and C_{11} alcohols cannot readily be explained unless the side chain is attached to a six-membered ring and is not α or β to the oxygen bridge. Structure (VI) is compatible with the

[10] Späth and Pailer, *Ber.*, 1940, **73**, 238; Späth, Pailer, and Gergely, *ibid.*, p. 795.

experimental results, but positive evidence for it is lacking. Attempts to obtain identifiable aromatic compounds, for example, by treating fumagillol or the C_{13} acid with concentrated hydrobromic or hydriodic acid, were inconclusive.

Experimental

Fumagillin was isolated from the metabolic products of *Aspergillus fumigatus* (strain A.61) as described by Goodall and Landquist,[11] and was purified by crystallisation from pentan-2-one.

Silica for chromatography was prepared as described by Martin and Synge.[12] Not all batches were suitable for separating the ozonolysis products of fumagillol, and a commercial brand of silica (Mallinckrodt) was also unsuitable for this purpose.

Hydrolysis of Fumagillin.—(*a*) Fumagillin (12·0 g.) was dissolved in 0·1N-sodium hydroxide (1·2 l.) under nitrogen, and after 4 hr. at room temperature the solution was filtered from a trace of flocculent material and extracted with ether (3 × 1 l.). Evaporation of the dried (Na_2SO_4) extract gave crude *fumagillol* (6·7 g.) which crystallised from light petroleum (b. p. 40—60°), giving 5·6 g., m. p. 54—56°, $[\alpha]_D^{24}$ −52° (1·27% in $CHCl_3$), b. p. 140°/0·02 mm. [Found: C, 68·0; H, 9·2; OMe, 10·9; OH (as active hydrogen), 6·7; *C*-Me, 7·1. $C_{16}H_{26}O_4$ requires C, 68·0; H, 9·2; OMe, 11·0; OH, 6·0; *C*-Me, 5·3% per Me group]. Evaporation of the petroleum mother-liquor gave syrupy fumagillol (0·8 g.), $[\alpha]_D$ *ca.* −40°. Re-extraction of the hydrolysis solution with ether after 20 hr. gave a trace more fumagillol (*ca.* 0·2 g.), and acidification precipitated octatetraene-1 : 8-dicarboxylic acid (4·6 g.).

(*b*) Fumagillin (10 g.), methanol (1 l.), and 40% aqueous sodium hydroxide (100 c.c.) were boiled under reflux for 1·5 hr., then cooled, and sodium octatetraene-1 : 8-dicarboxylate was filtered off. The filtrate was evaporated under reduced pressure at 30° and the residue was dissolved in water and extracted with ether (3 × 350 c.c.). Evaporation of the dried (Na_2SO_4) extract gave a syrupy *product*, $[\alpha]_D$ −33°, which was distilled at 0·005 mm. (bath-temp. 160—180°) (Found: C, 65·7; H, 10·3; OMe, 18·35, 18·5. $C_{17}H_{30}O_6$ requires C, 65·0; H, 9·55; 2OMe, 19·8%).

(*c*) Fumagillin (6·0 g.) in methanol (500 c.c.) was treated at 0° with 40% aqueous sodium hydroxide (5·0 c.c.). After 16 hr. at room temperature, the sodium salt was collected and dissolved in water, and the solution acidified to precipitate methyl hydrogen octatetraene-1 : 8-dicarboxylate (1·05 g.), m. p. 216—218°. Evaporation of the methanolic solution and extraction of the residue as in the foregoing experiment gave a syrup (3·1 g.), $[\alpha]_D$ −47° (Found: C, 65·6; H, 9·2; OMe, 18·3%).

Hydrogenated Derivatives.—(*a*) Fumagillol (0·75 g.) in water (100 c.c.) was hydrogenated over Adams platinum oxide catalyst, absorbing *ca.* 62 c.c. of hydrogen at N.T.P. in 30—35 min. (required for 1 mol. on M = 282, 59 c.c.). The filtered solution was extracted with ether, and the dried extract evaporated, giving *dihydrofumagillol* (0·57 g.) as a viscous syrup (Found: C, 69·5; H, 9·2; OMe, 10·3. $C_{16}H_{28}O_4$ requires C, 67·5; H, 9·85; OMe, 10·9%).

(*b*) Fumagillin (1·5 g.) in methanol (150 c.c.) was hydrogenated over platinum oxide, taking up 360 c.c. at N.T.P. in 45 min. (required for 5 mols., 375 c.c.). The filtered solution was evaporated under reduced pressure, giving a colourless syrup (1·4 g.; $[\alpha]_D$ −24° in MeOH) which slowly became jelly-like and showed signs of crystallising at the surface. Decahydrofumagillin (2·0 g.) was dissolved in 0·1N-sodium hydroxide (200 c.c.), and after 18 hr. at room temperature the solution was filtered and extracted with ether (4 × 200 c.c.). Acidification of the aqueous layer precipitated sebacic acid (0·76 g.), m. p. 133°. Evaporation of the dried (Na_2SO_4) extract gave dihydrofumagillol as a syrup (Found: C, 65·6; H, 9·7; OMe, 10·4%).

Functional Derivatives of Fumagillol.—Attempts to characterise fumagillol by treating it with 3 : 5-dinitrobenzoyl chloride, α-naphthyl *iso*cyanate, or fluoro-2 : 4-dinitrobenzene by standard procedures were unsuccessful. Keten did not acetylate fumagillol, and treatment with acetyl chloride and triethylamine in toluene gave a syrup, b. p. 165—170°/0·02 mm., which was not the required acetate (Found: C, 68·3; H, 8·7; OMe, 11·7; OAc, 16·7. Calc. for $C_{18}H_{28}O_5$: C, 66·6; H, 8·6; OMe, 9·55; OAc, 13·3%).

Oppenauer Oxidation.—Fumagillol (2·0 g.), aluminium *tert.*-butoxide (4·0 g.), freshly distilled *cyclo*hexanone (100 c.c.), and dry toluene (100 c.c.) were boiled under reflux for 3 hr., cooled, washed with ice-cold dilute hydrochloric acid and with water, dried (Na_2SO_4), and evaporated

[11] Goodall and Landquist, *Analyst*, 1955, **80**, 499.
[12] Martin and Synge, *Biochem. J.*, 1941, **35**, 1358.

under reduced pressure. Distillation at 0·02 mm. afforded a viscous yellow oil (1·1 g.) with a strong floral odour, b. p. 145—150° (Found: C, 67·6; H, 9·1; OMe, 9·2%). This product had only a weak absorption band at 1705 cm.$^{-1}$.

Reactions Characteristic of the Epoxide Group.—(*a*) Fumagillol (0·25 g.), dissolved in water (22·5 c.c.), was treated with N-hydrochloric acid (2·5 c.c.). The solution rapidly became turbid, and after 24 hr. it was extracted with ether (3 × 25 c.c.) and the extract was dried (Na_2SO_4) and evaporated. The syrupy chlorohydrin (0·15 g.) had $[\alpha]_D^{24}$ +29·4° (1·5% in $CHCl_3$) (Found: C, 56·0; H, 7·9; OMe, 9·3, 9·5; Cl, 7·7; active H, 0·52. Calc. for $C_{16}H_{27}O_4Cl$: C, 60·2; H, 8·46; OMe, 9·7; Cl, 11·15; active H, 0·314% per OH group). A sample obtained after a more prolonged reaction was distilled, b. p. 170°/0·02 mm. (Found: C, 58·8; H, 8·4; Cl, 11·3%).

(*b*) Aqueous solutions of fumagillol and sodium thiosulphate mixed at room temperature rapidly became alkaline to phenolphthalein. Fumagillol (1·5 g.), sodium thiosulphate (4·0 g.), and water (100 c.c.) were heated at 40—50° and kept just acid to phenolphthalein by titration with 0·212N-acetic acid. The end-point (23·1 ml.) was reached in about 40 min. (calc. for 1 epoxide group 25·0 ml.). The mixture was made strongly alkaline with sodium hydroxide, heated at 40° for 15 min., cooled, and extracted with ether (8 × 120 c.c.). The dried (Na_2SO_4) extract was evaporated under reduced pressure, giving the disulphide as a glass (Found: C, 60·1; H, 8·7; S, 8·8; OMe, 9·0. $C_{32}H_{54}O_8S_2$ requires C, 60·8; H, 8·55; S, 10·15; OMe, 9·8%). In a subsequent experiment, the alkaline aqueous reaction mixture deposited a trace of crystalline material on storage. This formed crystals, m. p. 152—153°, from aqueous ethanol (Found: C, 60·6; H, 7·9; S, 9·9%). The infrared spectrum did not show thiol absorption.

(*c*) Fumagillol (0·89 g.), magnesium bromide–diether complex (1·05 g.), and dry ether were boiled under reflux overnight. There was no loss of the epoxide reaction with thiosulphate. The ether was replaced by dibutyl ether and refluxing was continued for 6 hr., whereafter epoxide could no longer be detected. Water and ether were added to dissolve the magnesium bromide and the products of reaction, and the ether layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure, leaving a light brown syrup, $[\alpha]_D$ −29° (in $CHCl_3$), which showed infrared carbonyl absorption.

(*d*) Lithium aluminium hydride (1·0 g.) and dry ether (50 c.c.) were boiled under reflux for 2 hr., cooled, and treated gradually with fumagillol (1·0 g.) in dry ether (25 c.c.). The mixture was boiled for 3 hr., left overnight, and decomposed cautiously with water. The aqueous layer was separated and extracted with ether, and the combined ether solutions were dried (Na_2SO_4) and evaporated, giving a syrup which did not show an epoxide reaction with thiosulphate (Found: C, 66·1; H, 10·0; OMe, 10·8. Calc. for $C_{16}H_{28}O_4$: C, 67·5; H, 9·85; OMe, 10·9. Calc. for $C_{16}H_{30}O_4$: C, 67·1; H, 10·5; OMe, 10·8%). A similar product was obtained by desulphurising the disulphide (0·9 g.) with Raney nickel (5 g.) in boiling ethanol (30 c.c.) (Found: C, 65·3; H, 9·9; OMe, 11·0%).

(*e*) Fumagillol (0·5 g.) and N-sodium hydroxide (10 c.c.) were heated on the steam-bath until a neutralised sample no longer gave a reaction with sodium thiosulphate (48—64 hr.). The syrupy product (0·41 g.) was recovered by extraction with ether and dried at 90—100°/10 mm. (Found: C, 65·8, 65·6; H, 9·3, 8·9; OMe, 10·4. Calc. for $C_{16}H_{28}O_5$: C, 64·0; H, 9·33; OMe, 10·33%).

(*f*) Fumagillol (0·5 g.) and N/50-sulphuric acid (50 c.c.) were heated on the steam-bath until the epoxide reaction had disappeared (½—2 hr.), and the product (0·3 g.) was extracted with ether (Found: C, 63·5; H, 8·9; OMe, 11·1%). This material distilled mainly at 180°/0·01 mm. A similar hydrolysis carried out at room temperature took *ca.* 24 hr. for completion, and gave a product with a less complex infrared spectrum (Found: C, 60·2; H, 8·9; OMe, 11·3%).

Periodate Oxidation of Glycol from Treatment of Fumagillol with Cold 0·02N-Sulphuric Acid.—The glycol (0·8 g.), potassium metaperiodate (1·3 g.), and water (50 c.c.) were acidified with sulphuric acid and heated at 90—100°. Air was aspirated through the mixture and then through a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. After 3—4 hr. the precipitated 2 : 4-*dinitrophenylhydrazone* was collected, washed with dilute hydrochloric acid and water, dried, and crystallised from *cyclo*hexane. The crystals (40 mg.), m. p. 116—122°, were purified by chromatography on silica, with elution by *cyclo*hexane–benzene, and the main band was crystallised three times from *cyclo*hexane, giving 4 mg., m. p. 156—157° (Found: C, 51·4; H, 5·3. $C_{13}H_{14}O_4N_4$ requires C, 51·8; H, 5·0%). In a later experiment the crude 2 : 4-dinitrophenylhydrazone (48 mg.) was separated by chromatography on bentonite–kieselguhr [12] into acetone 2 : 4-dinitrophenylhydrazone (5 mg.), m. p. and mixed m. p. 123—125°, and the C_6 2 : 4-dinitrophenylhydrazone (11 mg.), m. p. 159—160° (Found: C, 52·3; H,

[12] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.

5·1%), ultraviolet absorption max. at 363 mμ (ε 21,900 in EtOH). When fumagillol was treated with periodic acid under the same conditions, only acetone 2 : 4-dinitrophenylhydrazone was isolated.

Ozonolysis of Fumagillol.—Fumagillol (5 g.), dissolved in dry ethyl acetate (100 c.c.), was cooled to −70° and treated with ozonised oxygen (*ca.* 7·5 l./hr.) until the solution became faintly blue and ozone issued freely from the reaction vessel. Excess of ozone was removed under reduced pressure and the solution was hydrogenated over pre-reduced palladium–calcium carbonate. The reaction was slow and the hydrogen uptake variable. The filtered solution was evaporated and acetone was isolated from the volatile portion as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126—127°. The residual gum was dissolved in ethyl acetate–benzene and chromatographed on 20 parts of silica. Elution with ethyl acetate–benzene gave two fractions, $[\alpha]_D$ +10—50° (2—3 g.) and $[\alpha]_D$ −20° to −30° (0·2—0·3 g.). A third fraction, $[\alpha]_D$ *ca.* −40° (0·2—0·9 g.) was eluted with ethyl acetate, and a fourth (0·3—1·4 g.) with ethanol. Crystallisation of the first fraction from ethyl acetate–light petroleum (b. p. 40—60°) gave the C_{13} aldehyde (0·8—1·8 g.), m. p. 153—155°, $[\alpha]_D$ +63° (1% in ethyl acetate), ultraviolet absorption max. at 220 mμ, infra-red absorption at 1685 cm.$^{-1}$ (very strong) (Found: C, 60·7; H, 7·5; OMe, 11·9. Calc. for $C_{13}H_{20}O_5$: C, 60·9; H, 7·8; OMe, 12·1%). Fractions 2 and 3 were mixtures of aldehyde and acid (infrared absorption at 1685 and 1715 cm.$^{-1}$), and fraction 3 slowly deposited crystals of the C_{13} *acid* which, crystallised from ethyl acetate–light petroleum, had m. p. 143—144°, $[\alpha]_D$ −65° (1·7% in ethyl acetate) (Found: C, 57·2; H, 7·2; OMe, 11·6%; equiv., 259, 266. $C_{13}H_{20}O_6$ requires C, 57·35; H, 7·35; OMe, 11·4%; equiv., 272). Fraction 4 was a brown gum, $[\alpha]_D$ *ca.* −35°. An inefficient separation of aldehyde was achieved by extracting the ethyl acetate solution of the ozonolysis products with aqueous sodium hydrogen carbonate. Crystalline aldehyde was recovered by evaporation of the ethyl acetate, but a considerable proportion was extracted into the aqueous layer with the acid and other by-products.

Ozonolysis of the C_{13} Aldehyde.—The aldehyde (2·0 g.) in dry ethyl acetate (100 c.c.) was ozonised at −70° until a faint blue colour indicated an excess of ozone. This was removed by aspirating air through the solution, and the ozonide was hydrogenated over palladium–calcium carbonate (very slow absorption of *ca.* 70 c.c. of hydrogen). The filtered solution was evaporated and the residue was heated at 60—65°/10 mm., the vapour passing through 2 : 4-dinitrophenylhydrazine hydrochloride solution. The latter gave a red-orange precipitate, m. p. 245—268°, which was crystallised twice from pyridine to give methylglyoxal bis-2 : 4-dinitrophenylhydrazone,[14] m. p. and mixed m. p. 294—296°. The non-volatile ozonolysis product (1·91 g.) was chromatographed in ethyl acetate–benzene on silica (45 g.), giving as successive fractions 0·13 g. of $[\alpha]_D$ −12°, 0·10 g. of $[\alpha]_D$ −10°, 0·09 g. of $[\alpha]_D$ −3°, 0·13 g. of $[\alpha]_D$ −19°, and, on change of solvent to pure ethyl acetate, 0·2 g. of $[\alpha]_D$ −9·5° and 0·73 g. of $[\alpha]_D$ −15° (all syrups or gums). This result was fairly reproducible, a better yield of the first fractions sometimes being obtained. The tail fraction resembled that from the ozonolysis of fumagillol in showing marked infrared absorption at *ca.* 1600 cm.$^{-1}$, and a broad carbonyl band at *ca.* 1720 cm.$^{-1}$. The first lævorotatory fractions, $[\alpha]_D$ *ca.* −10° (Found: C, 58·5, 58·2; H, 7·7, 7·9%), showed a narrow and intense infrared band at about 1700 cm.$^{-1}$ and appeared to be the most homogeneous of the ozonolysis products.

Reduction of the Ozonolysis Product.—The material (0·69 g.), $[\alpha]_D$ *ca.* −10°, from the ozonolysis of C_{13} aldehyde, lithium aluminium hydride (2·0 g.), and dry ether (150 c.c.) were boiled under reflux for 2 hr., left at room temperature overnight, treated cautiously with water, and just acidified with dilute sulphuric acid. The mixture was extracted with ether (3 × 150 c.c.), and the extract was dried (Na_2SO_4) and evaporated. The residue gradually afforded crystals (0·19 g.; m. p. 130—133°) which were collected, washed with ether, and crystallised twice from ethyl acetate to give an *alcohol* (0·04 g.), m. p. 162—164°, $[\alpha]_D$ −60° (0·8% in ethyl acetate) (Found: C, 58·5; H, 9·9; *C*-Me, 6·3. $C_{10}H_{20}O_4$ requires C, 58·8; H, 9·8; *C*-Me, 7·35%). The material in the mother-liquor and in the ethereal washings was partly separated by chromatography on silica or alumina (with ethyl acetate–benzene) into the compound of m. p. 162—164° and an *alcohol*, m. p. 121—122°, $[\alpha]_D$ −71° (in ethyl acetate) (Found: C, 57·4; H, 9·4. $C_{11}H_{20}O_5$ requires C, 56·8; H, 8·6%). Because of the inefficiency of the separation, the relative proportions of the two compounds could not be ascertained.

A similar reduction carried out on the corresponding first fractions (1·18 g.) from the ozonolysis of a mixture of C_{13} aldehyde and C_{13} acid (fraction 2 of the ozonolysis products of fumagillol) gave an uncrystallisable syrup (0·67 g.), $[\alpha]_D$ −18°, which was dissolved in ethyl

[14] Bülow and Seidel, *Annalen*, 1924, **439**, 55.

acetate–benzene, adsorbed on silica (12 g.), and eluted with ethanol. The fractions which crystallised on evaporation (0·06 g.) were recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), forming long prisms (0·027 g.) of a *product*, m. p. 124—126°, $[\alpha]_D$ −42° (in ethyl acetate) (Found: C, 59·5; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%).

Oxidation of the C_{10} *and the* C_{11} *Alcohol.*—(*a*) The alcohol, $C_{10}H_{20}O_4$, m. p. **162—164°** (5 mg.), in water (0·5 c.c.) was treated with 0·35 c.c. of a solution of chromium trioxide (1 g.) and sulphuric acid (1·5 g.) in water (50 c.c.). The mixture was shaken overnight and then extracted continuously with ether for 24 hr. Evaporation of the dried (Na_2SO_4) extract gave an oil (3·4 mg.). The other alcohols, $C_{11}H_{20}O_5$ (m. p. 121—122°) and $C_{10}H_{18}O_4$ (m. p. 124—126°), were oxidised similarly. The crude products were used for infrared spectroscopy.

(*b*) Periodate oxidations were studied with 2 mg. samples of the three alcohols, the periodate concentration being determined at intervals by ultraviolet spectroscopy.[15] In neutral solution no periodate was taken up in 3 hr.; in acid solution the alcohol $C_{10}H_{18}O_4$ consumed 0·15 mol. in 3 days and the others did not consume any.

N-Methyl-4-methylpent-3-enanilide. Methylaniline (15 g.) in dry ether (25 c.c.) was added to an ice-cold solution of methylmagnesium iodide (from 19·9 g. of methyl iodide and 3·4 g. of magnesium) in ether (100 c.c.). The mixture was stirred for 15 min. and then treated with ethyl 4-methylpent-3-enoate (9·8 g.) in ether (20 c.c.), stirred for 2·5 hr. at room temperature, and acidified with 2N-hydrochloric acid. The ether layer was separated, washed with water (2 × 25 c.c.), dried (Na_2SO_4), and distilled, giving the *product* (6·4 g.) as a yellow oil, b. p. 95—99°/0·25 mm. (Found: C, 76·6; H, 8·2; N, 7·4, 6·5. $C_{12}H_{17}ON$ requires C, 76·85; H, 8·35; N, 6·9%). The methylanilide (3 g.) in ether (30 c.c.) was stirred with lithium aluminium hydride (0·14 g.) at 0° for 21 hr., and the carbonyl compounds produced were isolated as 2 : 4-dinitrophenylhydrazones. Chromatography of these on bentonite–kieselguhr showed the presence of at least four compounds in amounts insufficient for characterisation.

Acyloin from Ethyl 4-Methylpent-3-enoate.—Ethyl 4-methylpent-3-enoate (22·3 g.) was added during 1 hr. to powdered sodium (7·23 g.) in ether (120 c.c.), and the mixture was stirred and boiled under reflux until almost all the sodium had dissolved (24 hr.). The mixture was then cooled in ice and made faintly acid by the careful addition of 50% sulphuric acid. The ether layer was separated, washed with aqueous sodium carbonate, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 0·8 g. of b. p. 60—100°/12 mm., 1·8 g. of b. p. 120—150°/12 mm., 1·4 g. of b. p. 160—200°/12 mm., and a considerable residue. Re-distillation of the second fraction gave 0·6 g., b. p. 120—130°/12 mm. (Found: C, 72·6; H, 10·0. Calc. for $C_{12}H_{20}O_2$: C, 73·47; H, 10·2%), and 0·1 g., b. p. 130—140°/12 mm. The use of xylene [16] instead of ether was not advantageous. The acyloin had infrared absorption bands at 3450 and 1710 $cm.^{-1}$.

Periodate Oxidations.—The foregoing acyloin fraction of b. p. 120—130°/12 mm. (0·4 g.) was reduced with lithium aluminium hydride (0·25 g.) in ether, and the glycol (0·4 g.) recovered from the ether after acidification was treated with periodic acid (2 g.) in water (100 c.c.) at 90—100°. Air was aspirated through the hot solution and then through a solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The dinitrophenylhydrazones were collected after several hours and separated by chromatography on bentonite–kieselguhr. The main fractions were acetone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126—127°, and 3-methylbut-2-enal 2 : 4-dinitrophenylhydrazone, m. p. 176—178°, ultraviolet absorption max. at 380 mμ (ε 27,400 in EtOH) (Found: C, 49·5; H, 4·7; N, 20·6. Calc. for $C_{11}H_{12}O_4N_4$: C, 49·8; H, 4·8; N, 21·2%). Braude and Jones [17] found the m. p. to be 179°, but higher values have been recorded. The same dinitrophenylhydrazones were isolated from periodate oxidation of other fractions from the acyloin condensation (without previous reduction with lithium aluminium hydride).

Ethyl 4-Methylpent-3-enthiolate.—Ethanethiol (3·6 g.), pyridine (5·0 g.), and benzene (15 c.c.) were stirred and treated with 4-methylpent-3-enoyl chloride (7·7 g.) in benzene (15 c.c.) at <30°. After 1 hr. pyridine hydrochloride was filtered off and the filtrate was washed with water, dried (Na_2SO_4), and distilled. The *thiol ester* (2·5 g.) boiled at 85—90°/16 mm. (Found: C, 60·3; H, 8·6. $C_8H_{14}OS$ requires C, 60·76; H, 8·85%).

Desulphurisation. Raney nickel (10 g.) was stirred under boiling acetone (50 c.c.) for 2 hr. Ethyl 4-methylpent-3-enthiolate (1·0 g.) was added and the mixture was stirred under reflux for 1 hr., filtered from nickel, and evaporated. The residual oil was suspended in warm water

[15] Dixon and Lipkin, *Analyt. Chem.*, 1954, **26**, 1092; Marinetti and Rouser, *J. Amer. Chem. Soc.*, 1955, **77**, 5345.
[16] Hansley, *J. Amer. Chem. Soc.*, 1935, **57**, 2303.
[17] Braude and Jones, *J.*, 1945, 498.

(50 c.c.), and air was drawn through the mixture to entrain first acetone and then 4-methylpent-2-enal, which was isolated as its **2** : 4-*dinitrophenylhydrazone*, scarlet needles, m. p. 203—204°, from ethyl acetate (Found : C, 51·3; H, 5·0; N, 19·7. $C_{18}H_{14}O_4N_4$ requires C, 51·8; H, 5·0; N, 20·1%), ultraviolet absorption max. at 381 mμ (ε 23,000 in EtOH).

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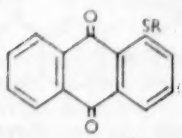
816. *Organic Sulphur Compounds. Part I. The Structure of Anthra-9 : 10-quinone-1-sulphenic Acid, its Derivatives, and Analogues.*

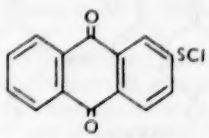
By J. A. BARLTROP and K. J. MORGAN.

The structures of anthra-9 : 10-quinone-1-sulphenic acid, its potassium salt, and its methyl ester are discussed. From an examination of the infrared and ultraviolet spectra of these and analogous compounds, the structure (I; R = OH) is deemed to be most probable for the acid.

ALTHOUGH derivatives of the sulphenic acids are well known,[1] only two such acids have been obtained as potassium salts and only one has been isolated as the free acid. Fries [2] prepared anthraquinone-1-sulphenic acid (I; R = OH) and its potassium salt, and 1-aminoanthraquinone-4-sulphenic acid has been obtained [3] as its potassium salt but not in the free state. Subsequently, many unsuccessful attempts were made [4] to synthesise other sulphenic acids. Even compounds closely analogous to anthraquinone-1-sulphenic acid appear not to be capable of isolation. Hydrolysis of anthraquinone-2-sulphenyl chloride (II) gave,[5] not the acid, but the corresponding sulphenic anhydride; similarly methyl fluorenone-1-sulphenate (III) led [6] only to a mixture of the sulphinic acid and the disulphide. However, several of the analogous selenenic acids have been synthesised.[7]



(I)



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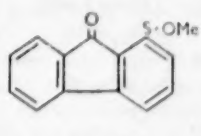

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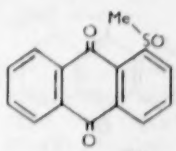
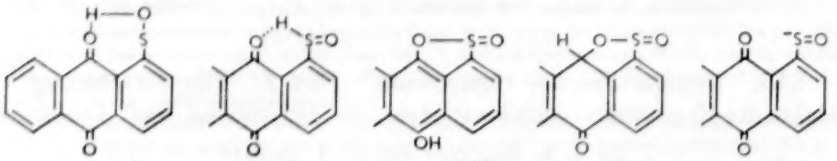


(IV)

A number of explanations of the apparently unique stability of anthraquinone-1-sulphenic acid have been advanced. Kharasch *et al.*[6,8] suggested that the stability is due to hydrogen bonding (cf. V). Since the site of the acidic hydrogen atom has not been adequately established [2,9] the equivalent structure (VI) has to be considered. Containing, as it does, an O···H–S hydrogen bond, the stability to be conferred by this structure is less [10] than that of the O···H–O bonded structure although some stabilisation

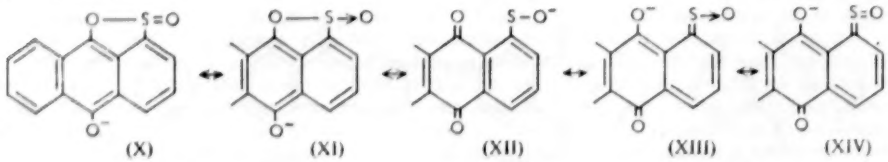
[1] Rathke, *Ber.*, 1870, **3**, 858; Zincke, *Ber.*, 1911, **44**, 769.
[2] Fries, *Ber.*, 1912, **45**, 2965.
[3] Fries and Schürmann, *Ber.*, 1919, **52**, 2182.
[4] Zincke and Baeumer, *Annalen*, 1918, **416**, 86; Zincke and Eismayer, *Ber.*, 1918, **51**, 751; Zincke and Farr, *Annalen*, 1912, **391**, 57; Zincke and Lenhardt, *ibid.*, 1913, **400**, 9; Zincke and Röse, *ibid.*, 1914, **406**, 103.
[5] Fries and Schürmann, *Ber.*, 1919, **52**, 2170.
[6] Kharasch and Bruicie, *J. Amer. Chem. Soc.*, 1951, **73**, 3240.
[7] Behaghel and Hofmann, *Ber.*, 1939, **72**, 582; Behaghel and Seibert, *Ber.*, 1933, **66**, 708; Behaghe and Müller, *ibid.*, 1935, **68**, 1540; 1934, **67**, 105; Jenny, *Helv. Chim. Acta*, 1952, **35**, 1429.
[8] Kharasch, Potempa, and Wehrmeister, *Chem. Rev.*, 1946, **39**, 269.
[9] Cf. Gutmann, *Ber.*, 1908, **41**, 1650.
[10] *Ann. Reports*, 1946, **43**, 153; Copley, Marvel, and Ginsberg, *J. Amer. Chem. Soc.*, 1939, **61**, 3161; Gordy and Standord, *ibid.*, 1940, **62**, 497.

might be expected from the replacement of a seven-membered chelate ring by a six-membered one. Lecher and Hardy [11] recently have suggested that the sulphenic acid is, in fact, the phenolic lactone (VII) of anthraquinol-1-sulphinic acid. The stability of a sulphinic ester may be presumed to be greater than that of a sulphenic acid; the acidity is assumed to be due to the free phenolic hydroxyl group. Such a quinol structure may be expected to equilibrate with the tautomeric oxanthrone structure (VIII) although this possibility was not considered by Lecher and Hardy, and under certain conditions the latter might well represent the sulphenic acid.



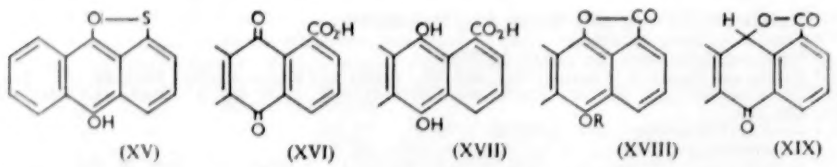
(V) (VI) (VII) (VIII) (IX)

Chemical evidence for the structure of the sulphenic acid is quite inconclusive. Reaction of the sulphenyl chloride (I; R = Cl) with methanol [2] gives the methyl ester (I; R = OMe), isomeric with, but distinct from, the methyl sulphoxide (IV). The methyl ester is readily hydrolysed by alkali to the blue-green salt of the sulphenic acid which on cautious acidification gives the red sulphenic acid. The acid reacts [2] with hydrogen chloride to give the sulphenyl chloride (I; R = Cl) and with hydrogen bromide to give the corresponding sulphenyl bromide. It may be noted that the reverse reaction, the direct hydrolysis of the acid chloride to the acid, leads to decomposition products. The free acid is methylated by methyl sulphate [2] to the ester (I; R = OMe); the alkali-metal salts treated similarly yield [2] the sulphoxide (IV). Sulphinic acids also give esters and sulphones by alkylation of, respectively, the acid and the salt.[12] This, and the colour of the salts, suggest that in the sulphenate anion a significant negative charge resides on the sulphur atom (IX) rather than on the oxygen atoms as is written by Lecher and Hardy [11] (X—XIV).



(X) (XI) (XII) (XIII) (XIV)

The structure proposed by Lecher and Hardy [11] can be applied not only to the sulphenic acid but also to certain analogous compounds. In particular, the structure of 1-mercaptoanthraquinone (I; R = H) might be written as the sulphenic lactone (XV), for in alkaline solution 1-mercaptoanthraquinone gives a blue-violet solution, whereas anthraquinone-1-sulphenic acid similarly gives a blue potassium salt. This analogy, however, may not be sound since a similar blue colour in alkaline solution is given by 2-mercaptoanthraquinone.



(XV) (XVI) (XVII) (XVIII) (XIX)

A series of carboxylic acid derivatives of anthracene exists which offers more reliable structural analogies to the possible structures of anthraquinone-1-sulphenic acid.

[11] Lecher and Hardy, *J. Org. Chem.*, 1955, **20**, 475.
[12] Rheinboldt, Mott, and Motzkus, *J. prakt. Chem.*, 1932, **134**, 257.

Specimens of these, namely, (XVI), (XVII), and (XVIII; R = H and Ac), were prepared with the intention of using them as spectral models. The free quinol (XVII) is autoxidised so rapidly that it was useless for this purpose. The lactone (XVIII; R = H) was not stable, but by rapid working it was possible to record its ultraviolet spectrum; in particular, the change red (acid) ⟶ blue (salt), similar to that of the sulphenic acid, was observed. The spectral data so obtained were compared with those obtained from the free sulphenic acid, its derivatives, and other analogous systems (Tables 1 and 2).

Infrared Spectra.—Flett [13] has examined the infrared spectra of a large number of anthracene derivatives. As might be expected, anthraquinols show no absorption in the carbonyl region but exhibit a band in the region associated with a hydrogen-bonded O–H stretching frequency (3300 cm.$^{-1}$).

Many anthraquinones show one band in the carbonyl region between 1675 and 1686 cm.$^{-1}$. The infrared spectra of anthraquinone-1-sulphenic acid, its potassium salt, and its methyl ester all show a strong band in the carbonyl region (1664—1672 cm.$^{-1}$); so also does 1-mercaptoanthraquinone (Table 1). This serves strongly to confirm that the methyl sulphenate has the anthraquinone structure (I; R = OMe). In addition, the sulphenic derivatives exhibit a peak of medium-low intensity at 1626—1634 cm.$^{-1}$, which in the case of the acid may well be due to hydrogen bonding: a twin peak at 1636 cm.$^{-1}$ is observed [13] in 1-hydroxyanthraquinone, but the occurrence of a similar band in the ester and also, weakly, in the mercapto-compound, makes its significance doubtful.

A recent analysis [14] of the spectra of aromatic sulphinic acids identifies three groups of absorption band prominent in the spectra of their esters: 1126—1136 cm.$^{-1}$ (S=O

TABLE 1. *Infrared spectra.*

Anthraquinone derivative	Medium	Band frequencies (in cm.$^{-1}$) OH	CO	Other bands		
1-Sulphenic acid	Nujol mull	3125 (w) (broad)	1672 (s)	1631 (w)	1134 (w)	962 (m)
	$CHCl_3$ (conc.)	3330—3510 (w)	1672 (s)	1634 (m)	1136 (w)	960 (m)
	$CHCl_3$ (dil.)	3510 (w)	1669 (s)	1631 (m)	1135 (m)	960 (m)
Potassium 1-sulphenate ...	Nujol mull	—	1678 (s)	—	1122 (w)	963 (m)
Methyl 1-sulphenate	Nujol mull	—	1664 (s)	1626 (m)	1130 (m)	961 (m)
1-Mercapto [a]	Nujol mull	—	1669 (s)	1639 (w)	1139 (w)	952 (w)

[a] The compound shows no SH band in the region 2600—2550 cm.$^{-1}$.

stretching), 960 cm.$^{-1}$ (S–O stretching), and a broad band near 752 cm.$^{-1}$. An absorption band at 963—960 cm.$^{-1}$ is observed in our three sulphenic compounds, another also at 1122—1136 cm.$^{-1}$. Both these bands are here considerably weaker than those reported by Detoni and Hadzi [14] and it seems that little significance can be attached to them in these circumstances. This is particularly true of the band at 1136 cm.$^{-1}$, which occurs in the approximate position of bands found in polysubstituted aromatic compounds and also of bands due to certain aromatic ketones. It may be noted that 1-mercaptoanthraquinone shows weak bands at 1139 and 952 cm.$^{-1}$.

The variation of the position and form of the band corresponding to the O–H stretching vibration in the sulphenic acid is of interest. Appearing as a broad band of low intensity at about 3125 cm.$^{-1}$ in the solid state, it occurs in solution as a sharp, but still weak band at 3509 cm.$^{-1}$. It seems that this is due to a polymeric association through intermolecular hydrogen bonds which on dissolution and dilution break and re-form to give a singly bridged intramolecular hydrogen bond, C=O · · · H–O. The former is known [15a] to give rise to broad-banded absorption in the region 3200—3450 cm.$^{-1}$. If, as is argued below, the sulphenic acid is best represented as R·S·OH, any intramolecular hydrogen bonding (V) could not be chelate-conjugated and would be expected [15b] to show a sharp band between 3450 and 3570 cm.$^{-1}$. [The alternative structure (VI) should not show O–H bands.] Anthraquinol exhibits [13] a broad band at 3300 cm.$^{-1}$.

[13] Flett, *J.*, 1948, 1441.
[14] Detoni and Hadzi, *J.*, 1955, 3163.
[15] (*a*) Bellamy, "Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1954, p. 88; (*b*) *op. cit.*, p. 89.

TABLE 2. *Ultraviolet absorption spectra.*

Anthraquinone derivative	λ (mμ)	ε	λ (mμ) *	ε	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε
1-Carboxylic acid	251	36,000	[272]	12,600	—	—	329	4700	—	—	—	—	—	—	—	—
Potassium 1-carboxylate	250	38,000	[272]	13,000	—	—	335	4100	—	—	—	—	—	—	—	—
Methyl carboxylate	254	45,000	[270]	19,600	[305]	4140	324	4700	—	—	—	—	—	—	—	—
1-Sulphinic acid	256	31,000	[273]	10,000	—	—	328	3900	—	—	—	—	—	—	—	—
Methyl 1-sulphoxide	250	—	[270]	—	[300]	—	320	—	—	—	—	—	—	—	—	—
1-Mercapto-	251	30,200	[270]	12,000	[300]	3200	[315]	2900	—	—	—	—	—	—	—	—
Potassium 1-mercaptide	249	35,700	[270]	14,000	[300]	4000	315	4100	395	2100	—	—	—	—	—	—
1-Sulphenic acid	248	43,200	[270]	15,800	—	—	314	5500	—	—	—	—	—	—	—	—
Potassium 1-sulphenate	250	41,000	[270]	14,800	[306]	6300	317	6200	—	—	—	—	—	—	—	—
Methyl 1-sulphenate	247	29,400	[266]	13,800	304	4900	[325]	2760	—	—	—	—	—	—	—	—
9 : 10-Diacetoxyanthracene	255	235,000	—	—	—	—	354	8500	372	12,800	393	11,400	—	—	—	—
Lactone acetate of 1-carboxyanthraquinol (XVIII; R = Ac)	237	23,500	262	73,400	—	—	—	—	—	—	—	—	—	—	—	—
Lactone of 1-carboxyanthraquinol (XVIII; R = H)	239	21,200	265	19,400	284	25,000	306	8700	340	572	368	519	488	1570	790	7600
Potassium salt (XVIII; R = K)	255	28,500	305	17,000	[340]	5700	390	3800	—	—	—	—	—	—	—	—
Anthrone	260	22,800	[293]	7400	[303]	4800	[335]	867	368	536	—	—	—	—	—	—
10-Methyloxanthrone	275	20,800	[303]	5000	—	—	—	—	—	—	—	—	—	—	—	—
Autoxidation product from 1-carboxyanthraquinol	248	34,000	[270]	13,600	305	2700	330	4800	—	—	—	—	—	—	—	—
Autoxidation product from lactone (XVIII; R = H)	252	27,300	[268]	12,200	316	1900	—	—	—	—	—	—	—	—	—	—

All spectra were measured on methanol solutions. Except for the lactone (XVIII; R = H), in which measurements were extended into the visible region, all spectra were measured in the range 200—400 mμ.

* Data in square brackets refer to points of inflexion.

Ultraviolet Spectra.—The ultraviolet spectra of anthraquinones have been widely studied.[16] Four bands appear to characterise the anthraquinone nucleus: two benzenoid bands at 246—257 mμ (ε 29,000—48,000) and at 312—333 mμ (ε 2900—7000), and two quinonoid bands at 261—266 mμ (ε 12,400—23,000) and at 270—277 mμ (ε 11,000—18,400). The bands at 265 mμ are frequently absent but the other three bands appear regularly in the spectra of a wide range of substituted anthraquinones; the nature of the substituent has little effect on the position of these bands. There are also bands in the visible region, the position and intensity of which vary largely with the substituent.

The data presented in Table 2 for substances of known anthraquinonoid structure (1—8) conform to this analysis. The band at 265 mμ is uniformly absent. The other absorption bands fall within the limits 247—256 mμ (ε 29,000—45,000), 266—273 mμ (ε 12,000—19,000), and 315—335 mμ (ε 2900—4700). The spectra of the sulphenic acid and its potassium salt show bands within these limits: 248, 250 mμ (ε 43,200, 41,000), 270 mμ (ε 15,800, 14,800), and 314, 317 mμ (ε 5500, 6100). These data strongly support the quinonoid structure of the sulphenic acid and its salt.

A comparison of these results with the spectral data for anthraquinols serves further to support this. The spectrum of 9:10-diacetoxyanthracene shows one peak of very high intensity at 255 mμ (ε 236,000). Replacement of one acetoxy-group by a five-membered lactone ring (XVIII; R = Ac) causes some reduction in intensity and a simultaneous shift in the position of the maximum absorption (262 mμ; ε 73,400). When the second acetyl group is removed to leave the free phenolic lactone (XVIII; R = H), a structure analogous to Lecher and Hardy's sulphenic acid formulation (VII),[11] the spectrum undergoes a complete change: the absorption maximum at 265 mμ is of greatly reduced intensity (ε 19,400) and there appear new maxima at 284, 306, 340, and 368 mμ, corresponding closely in position to those found for anthrone, *viz.*, 260, 293, 303, 335, and 368 mμ. (Martin [17] finds for anthrone: $\lambda_{max.}$ 260, 292, 299, 304, 349, 368 mμ.) It may be deduced from this that the equilibrium between the quinol (XVIII; R = H) and the oxanthrone (XIX) structure lies well on the side of the latter in solution in methanol. It may be noted that the positions of the absorption maxima of the lactone, here recorded, differ markedly from those reported by Scholl and Böttger,[18] *viz.*, 258 (ε 1600), 272 (ε 1600), and 351 mμ (ε 2250). Solutions of the lactone autoxidise rapidly, and after short standing a solution of the lactone (XVIII; R = H) showed absorption maxima at 252 (ε 27,300), 268 (ε 12,200), and 316 mμ (ε 1900), values which are more closely related to those of Scholl and Böttger and strongly suggest a quinonoid structure. Even more readily oxidised is the potassium salt of the lactone (XVIII; R = K), the blue solution of which is completely decolorised in a few minutes. By working rapidly, it was possible to obtain an approximate spectrum of this salt; it shows a similarity to that of the parent lactone. The free 1-carboxyanthraquinol (XVII) was too unstable to permit any measurements: its autoxidation products appear to be quinonoid.

The absorption of many of these anthracene compounds extends into the visible region; in particular, the potassium salts of anthraquinone-1-thiol, anthraquinone-1-sulphenic acid, and of the phenolic lactone (XVIII, R = K) all produce blue solutions. Although little of any general structural significance can be deduced from measurements in this region, for the positions of maxima and the values of extinction coefficients are sensitive functions of the substituent groups, yet a direct comparison of spectra can be illuminating, and it was hoped to obtain data which would enable a decision to be made between the alternative R·S·OH and R·SH:O structures for the sulphenic acid by comparing its spectrum with those of the ester (I; R = MeO) and the isomeric sulphoxide (IV). The latter was too sparingly soluble in methanol to permit direct comparison, but maxima were indicated at 250, 270, 300, and 320 mμ. However, Jenny [19] has compared the spectra of the ester and the sulphoxide in chloroform solution over the range 300—600 mμ. The

[16] Morton and Earlam, *J.*, 1941, 159; Allen, Wilson, and Frame, *J. Org. Chem.*, 1942, **7**, 169; Sprait, *Rec. Trav. chim.*, 1949, **68**, 325; Hartman and Lorenz, *Z. Naturforsch.*, 1952, **7**, 360; Peters and Sumner, *J.*, 1953, 2101.
[17] Martin, *Ann. Combustibles liquides*, 1937, **12**, 97; Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[18] Scholl and Böttger, *Ber.*, 1930, **63**, 2128.
[19] Jenny, *Helv. Chim. Acta*, 1952, **35**, 845.

the charged entity (XX or XXI) which then abstracts electrons from another molecule of

ester had maxima at 311 (ε 6300) and 465 mμ (ε 6300); the sulphoxide at 349 (ε 5000) and 420 mμ (ε 800). The position of these bands and the extinction coefficient of the longer-wavelength band make it probable that the sulphenic acid, $\lambda_{max.}$ 314 mμ (ε 5530) and 470 mμ (ε 4500), has a structure corresponding to that of the ester, *i.e.*, R·S·OH. This conclusion is supported by infrared spectra.

The presence in many of these spectra of low-intensity peaks around 300—310 mμ may be noted. These occur mainly as points of inflexion over a range where the gradient of the spectral curve is small, so it is difficult to assess their position and intensity accurately; their significance is equally difficult to determine.

Conclusions.—Of the four structures (V)—(VIII) which have been advanced for anthra-9 : 10-quinone-1-sulphenic acid, Lecher and Hardy's formulation (VII),[11] with its tautomeric modification (VIII), can be immediately discarded, primarily because the infrared spectrum of the sulphenic acid shows the presence of a carbonyl group which is inexplicable in terms of (VII), and a hydroxyl group, which is non-existent in (VIII). In order to explain the infrared data on a tetracyclic structure, one would have to postulate that the sulphenic acid consisted of a tautomeric mixture of (VII) and (VIII), and this possibility is excluded because the ultraviolet spectrum shows a total absence of the anthrone bands which are such a prominent feature of the spectrum of the analogous carboxylic lactone (XVIII; R = H) ⇌ (XIX). Furthermore, formula (VIII) can be regarded as that of an anthrone or as an oxanthrone, and Flett [13] finds that anthrones substituted in the 4-position by H, Cl, MeO, NH_2, or OH have C=O bands in the range 1645—1658 cm.$^{-1}$ (measured in the solid state) and that oxanthrones substituted in the 4-position by H, Cl, or MeO have C=O bands at about 1652 cm.$^{-1}$ (solid state). The fact that the sulphenic acid absorbs at 1672 cm.$^{-1}$ provides further evidence against the oxanthrone structure (VIII) and hence against Lecher and Hardy's formulation (VII).

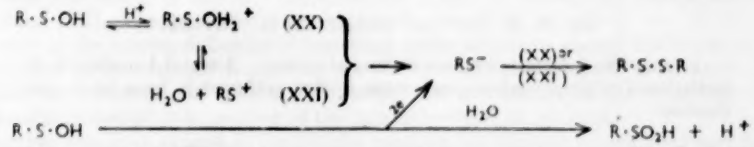
We are thus led to conclude that the sulphenic acid must be an anthraquinone derivative (V) or (VI). The purely chemical evidence of its synthesis, general properties, and ease of hydrolysis, strongly suggests that the methyl anthraquinonesulphenate possesses the anthraquinone structure (I; R = MeO) and the infrared spectrum of the substance, supported by the close relation between the ultraviolet spectra of the ester and the other 1-substituted anthraquinones in Table 2, provides overwhelming support. Once this is accepted, then the obvious spectroscopic parallel between the ester and the salt and the sulphenic acid indicates that the last must also be an anthraquinone derivative. The presence of an OH group in the molecule (intramolecularly hydrogen-bonded by a single non-chelate bridge according to the infrared spectrum) then further suggests that the sulphenic acid must exist predominantly, if not exclusively, in the form (V) in dilute solution. There can be no doubt that the 1-mercaptoanthraquinone has the conventional structure (I; R = H).

It seems probable that the selenenic acids have similar structures, their superior stability being due to the reluctance of selenium to assume the higher valency states, especially in combination with oxygen.

The stability of anthraquinonesulphenic acid remains unique. Flett [13] suggests that intramolecular hydrogen bonding stabilises 1 : 4-dihydroxyanthraquinone to the extent of about 7·5 kcal. per hydroxyl group. Such stabilisation will of course be weaker in the sulphenic acids whether they contain the non-chelate O···H–O or the conjugated O···H–S bond.[10] Nevertheless, stabilisation arising from this source must be important since the only known selenenic acids [7] are those which can be stabilised by hydrogen bonding, *e.g.*, 2 : 4-dinitrobenzene-, *o*-nitrobenzene-, and 1-anthraquinone-selenenic acids, and since the non-intramolecularly bonded anthraquinone-2-sulphenic acid cannot be prepared.

This factor is insufficient by itself to explain the instability of sulphenic acids other than the 1-anthraquinonyl compound. The crux of the matter appears to be the relative resistance of anthraquinonesulphenic acid to dismutation to disulphide and sulphinic acid, the reaction apparently responsible for the spontaneous destruction of many of the other sulphenic acids. Unpublished results from this laboratory have shown that the dismutation of anthraquinone-1-sulphenic acid is acid-catalysed and may depend on the formation of

the charged entity (XX or XXI) which then abstracts electrons from another molecule of the sulphenic acid :



On this view, electron-attracting groups should stabilise the sulphenic acids, by retarding the formation of (XX or XXI). However, if the substituents are too powerful, then the electron-deficient sulphur atom of the sulphenic acid itself begins to accept electrons so that dismutation can again take place. Seen in these terms, stable sulphenic acids are delicately poised systems, possessing substituents sufficiently electron-attracting to inhibit dismutation through the ions (XX or XXI), yet not so strongly attracting as to induce dismutation through the electron deficiency of the SOH grouping itself.

Experimental

Anthraquinonesulphenic acid, its potassium salt, and its methyl ester, anthraquinone-1-sulphinic acid and methyl anthraquinone-1-sulphoxide were prepared from 1-aminoanthraquinone and purified according to Fries.[18] Anthraquinone-1-carboxylic acid,[20] most conveniently crystallised from nitric acid, was converted into its methyl ester, in good yield, by the action of diazomethane. Anthraquinol-1-carboxylic acid,[21] its lactone,[22] and its lactone acetate [21, 22] were prepared from the anthraquinonecarboxylic acid. The dark red quinol acid was oxidised immediately on exposure to air, becoming ashy-grey. The lactone, also red, was considerably more stable, but the blue colour of solutions of its potassium salt lasted only for a few seconds unless special precautions were taken. By use of methanol from which the oxygen had been expelled by prolonged passage of a stream of oxygen-free nitrogen, the duration of the colour was extended sufficiently to enable a small number of spectroscopic observations to be made. By using a large number of solutions, each measured over a small spectral range, an approximate spectrum of the salt was obtained. The lactone acetate was stable.

Specimens of 9 : 10-diacetoxyanthracene, anthrone, and methyloxanthrone were kindly supplied by Mr. M. L. Burstall. Ultraviolet spectra were measured in solution in methanol on a Unicam spectrophotometer. Infrared spectra were determined with a Perkin-Elmer spectrophotometer by Mr. F. J. Hastings, for whose technical assistance the authors express their thanks. This investigation was conducted during the tenure by one of us (K. J. M.) of a Senior Hulme Scholarship of Brasenose College, Oxford.

Dyson Perrins Laboratory, South Parks Road, Oxford. [*Received, May 16th*, 1956.]

[18] Ullmann and van der Schalk, *Annalen*, 1912, **388**, 199.
[21] Scholl, Böttger, and Hass, *Ber.*, 1929, **62**, 616.
[22] Scholl, Renner, and Mayer, *ibid.*, p. 1278.

817. *Some Derivatives of 2 : 3-Dihydroxynaphthalene.*

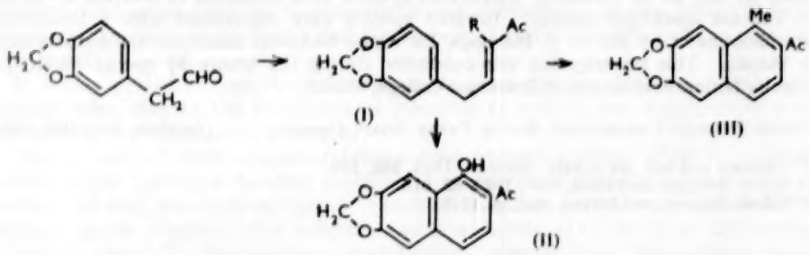
By F. H. Howell and D. A. H. Taylor.

2-Acetyl-6 : 7-dimethoxy-1-methylnaphthalene, 2-acetyl-1-methyl-6 : 7-methylenedioxynaphthalene, and some related compounds have been synthesised.

2-Acetyl-6 : 7-dihydroxy-1-methylnaphthalene was required for a projected synthesis. This compound has not yet been prepared, although derivatives have now been made by several methods.

1-Methylnaphthalene-2-carboxylic acid has been prepared by cyclisation and dehydrogenation of ethyl β-phenethylacetoacetate [1] and in the first instance an attempt was made to extend this method to the preparation of the dimethoxy-compound. 3 : 4-Dimethoxyphenethyl alcohol, prepared by Fulton and Robinson [2] by Bouveault–Blanc reduction of ethyl homoveratrate, was obtained in higher yield by the reduction of this ester with lithium aluminium hydride, and, better, by interaction of 3 : 4-dimethoxyphenyl-lithium and ethylene oxide. The lithium derivative was prepared by the interaction of 4-bromoveratrole and butyl-lithium, and the essential condition [3] for the interchange was that reaction should be carried out below −50°: at higher temperatures 3 : 4 : 3′ : 4′-tetramethoxydiphenyl was obtained, at −10° in >80% yield. The alcohol was converted by thionyl chloride into 3 : 4-dimethoxyphenethyl chloride, which however with ethyl sodioacetoacetate gave only a low-boiling liquid, probably 3 : 4-dimethoxystyrene.

An alternative route to the required keto-ester appeared to be condensation of homoveratraldehyde with ethyl acetoacetate, followed by hydrogenation: alternatively, cyclisation of the condensation product before hydrogenation might lead directly to a naphthalene derivative. It was found more convenient to use homopiperonaldehyde, which Erdtman and Robinson have prepared [4] by lead tetra-acetate oxidation of safrole glycol, itself made by permanganate oxidation of safrole. We found it easier experimentally to use performic acid for the hydroxylation of safrole. Homopiperonaldehyde condensed readily with ethyl acetoacetate in the presence of pyridine, but the product (I; R = CO_2Et), on distillation in a high vacuum, lost ethanol and gave a substance which is considered to be 2-acetyl-1-hydroxy-6 : 7-methylenedioxynaphthalene (II): it is insoluble in alkali but gives a green ferric chloride colour.



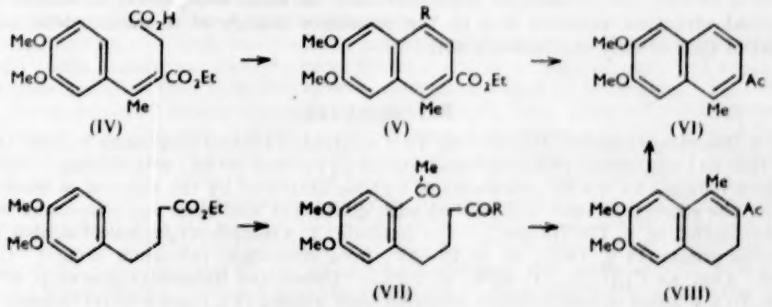
To avoid this cyclisation, the symmetrical product (I; R = Ac) from homopiperonaldehyde and acetylacetone was prepared. This proved to be stable on distillation, but was rather resistant to cyclisation, being unattacked by formic acid, or by toluene-*p*-sulphonic acid or iodine in boiling benzene, and was decomposed by sulphuric acid or by

[1] Auwers and Möller, *J. prakt. Chem.*, 1925, **109**, 148.
[2] Fulton and Robinson, *J.*, 1933, 1463.
[3] Calvin, Heidelberger, Reid, Talbert, and Yankwich, "Isotopic Carbon," John Wiley and Sons, New York, 1949, p. 183.
[4] Erdtman and Robinson, *J.*, 1933, 1530.

bases. However, on treatment with hydrogen chloride in chloroform a substance, m. p. 134°, was obtained which had lost one molecule of water, no longer gave a ferric chloride colour, and was stable to alkali. The structure, 2-acetyl-1-methyl-6 : 7-methylenedioxynaphthalene (III), is proposed for this compound.

In view of the known difficulty of removing methylenedioxy-groups this work was now repeated with methyleugenol in place of safrole. Homoveratraldehyde condensed readily with ethyl acetoacetate and with acetylacetone, but in contrast to the behaviour of the methylenedioxy-compounds, neither of the products could be cyclised.

Attention was next turned to the Stobbe reaction between acetoveratrone and diethyl succinate. The half-ester (IV) was obtained in high yield in the presence of sodium hydride. The crude product, when refluxed with acetic anhydride and sodium acetate, gave a moderate yield of a crystalline product. In view of the known high reactivity of veratrole derivatives in positions 4 and 5, this product is taken to be ethyl 4-acetoxy-6 : 7-dimethoxy-1-methylnaphthalene-2-carboxylate (V; R = OAc). Treatment with sodium



ethoxide gave the free phenol. In order to remove the phenolic hydroxyl group, this compound was converted into the toluene-*p*-sulphonate, which was refluxed with Raney nickel in ethanol (cf. Kenner and Murray [5]), but gave only a small yield of substance giving analytical figures for the expected ethyl 6 : 7-dimethoxy-1-methylnapthalene-2-carboxylate (V; R = H), the major part of the ester being hydrolysed back to the phenol.

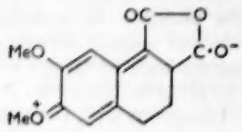
The ethyl ester (V) was converted into the acid chloride, which with dimethylcadmium gave 2-acetyl-6 : 7-dimethoxy-1-methylnaphthalene (VI), identical with a specimen prepared more conveniently from 3-(2-acetyl-4 : 5-dimethoxyphenyl)propyl methyl ketone (VII; R = Me). For the preparation of this ketone, ethyl γ-3 : 4-dimethoxyphenylbutyrate was acetylated by the Friedel–Crafts method, the product being isolated as the acid (VII; R = OH) in 60% yield (an attempt was made to cyclise the ethyl ester of this compound, but it was unchanged by sodium ethoxide in ethanol). The derived acid chloride (VII; R = Cl) with dimethylcadmium formed the methyl ketone (VII; R = Me) which was cyclised by sodium ethoxide to 2-acetyl-3 : 4-dihydro-6 : 7-dimethoxy-1-methylnaphthalene (VIII) in 60% overall yield from the acid.

The intermediate diketone (VII; R = Me) could be isolated if desired, although this was inadvisable as it was rather soluble; it could then be cyclised with sodium ethoxide or with acid in quantitative yield. The dihydronaphthalene was dehydrogenated by sulphur or palladium to the required naphthalene derivative (VI). Unfortunately the methoxy-groups in this compound have only been removed under conditions which lead to extensive decomposition.

6 : 7-Dimethoxynaphthalene-1 : 2-dicarboxylic acid has also been prepared. Ethyl γ-3 : 4-dimethoxyphenylbutyrate was condensed with diethyl oxalate, and the product cyclised with sulphuric acid in phosphoric acid, yielding the dihydronaphthalene which was

[5] Kenner and Murray, *J.*, 1949, S 178.

dehydrogenated with sulphur. 3 : 4-Dihydro-6 : 7-dimethoxynaphthalene-1 : 2-dicarboxylic acid, formed by hydrolysis of the ester, crystallised in yellow needles which readily formed the anhydride. This change was most striking, as the anhydride, previously prepared by Fieser and Hershberg [6] and by Bruckner,[7] has an intense red colour. In the fully aromatic series the anhydride [7] was again more deeply coloured than the ester, but not nearly so intensely. The colour of the anhydride is probably concerned with the formation of the extended quinonoid system (IX), in which it might be expected that the more strongly electron-attracting anhydride substituent would give rise to a more intense colour than the ester. This cannot, however, be the whole answer, otherwise the ketone (VIII) would be yet more strongly coloured, which is not so. Cross-conjugation due to the second carbonyl group may also assist, but this is again not more than a part of the answer. It seems probable that the inclusion of the carbonyl group in a ring may be a major contributing factor. The lower intensity of colour in the fully aromatic compounds can be explained since in these compounds formation of the quinonoid structure involves loss of the resonance energy of a naphthalene nucleus, instead of that of only one benzene ring.



(IX)

Experimental

3 : 4-*Dimethoxyphenethyl Alcohol.*—(*a*) To a solution of lithium aluminium hydride (8 g.) in ether (250 ml.) was added ethyl homoveratrate (31 g.) in ether (50 ml.) with stirring. The whole was then refluxed for 0·5 hr. and excess of hydride destroyed by the addition of methanol in ether. The ethereal solution was washed with dilute acid and water and evaporated and the residue distilled (b. p. 178°/16 mm.). The distillate, 3 : 4-dimethoxyphenethyl alcohol, formed colourless prisms (18 g. 72%), m. p. 42—43°, from ether–light petroleum (Found : C, 66·2; H, 7·6. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%). Fulton and Robinson [8] give m. p. 48°.

(*b*) To a solution of butyl-lithium prepared from lithium (5 g.) and *n*-butyl bromide (45 g.) in ether (400 ml.) was added at −60°, with stirring, 4-bromoveratrole (70 g.) in ether (200 ml.). The thick suspension obtained was allowed to warm to about −40° and ethylene oxide (40 g.) added slowly, the temperature being kept below about −10°. Then the mixture was stirred for 1 hr. at 0°, and washed with hydrochloric acid and with water, and the product distilled. After crystallisation from ether–light petroleum the alcohol (42 g., 73%) was obtained with m. p. 43°.

3 : 4 : 3′ : 4′-*Tetramethoxydiphenyl.*—To a solution of butyl-lithium from lithium (3·5 g.) and butyl bromide (34 g.) in ether (200 ml.) was added at 0° 4-bromoveratrole (50 g.) in ether (100 ml.). Ethylene oxide (20 g.) was then added, and the solution kept at 0° for 1 hr., washed with hydrochloric acid and with water, and evaporated. The residue, crystallised from ethanol, gave 3 : 4 : 3′ : 4′-tetramethoxydiphenyl (21 g.), m. p. 133—134° (Found : C, 70·3; H, 6·5. Calc. for $C_{16}H_{18}O_4$: C, 70·1; H, 6·6%).

Safrole Glycol.—Safrole (158 g.) was stirred with 90% formic acid (450 ml.) and 30% hydrogen peroxide (140 ml.) at <25°. After 24 hr. the solution was heated to 40° and stirred until per-acid was no longer detectable (about 3 hr.). The acid was then evaporated in a vacuum on the steam-bath, and the residue hydrolysed for a few minutes with an excess of warm 20% aqueous potassium hydroxide. The solution was then continuously extracted for 12 hr. with ether, the ether evaporated, and the residue distilled. After safrole (44 g.) had been removed at 125°/15 mm. the pressure was reduced and safrole glycol distilled at 176°/0·15 mm. Crystallisation from benzene gave 69 g. (35%) of glycol, m. p. 69°.

Homopiperonaldehyde.—Safrole glycol (45 g.) in benzene (76 ml.) was added to lead tetra-acetate (103 g.) in benzene (455 ml.). After 2 hr. (occasional shaking), the solution was filtered from precipitated lead diacetate, washed with sodium hydrogen carbonate solution and with water, and evaporated. Homopiperonaldehyde (31 g., 82%) distilled at 147/0·8 mm. (n_D^{26} 1·5521).

2-*Acetyl*-6 : 7-*methylenedioxy*-1-*naphthol* (II).—Homopiperonaldehyde (31 g.), ethyl acetoacetate (72 ml.), pyridine (72 ml.), and piperidine (1 ml.) were heated on the steam-bath for 4 hr. The volatile matter was removed at 14 mm., and the residue distilled in a high vacuum. 2-*Acetyl*-6 : 7-*methylenedioxy*-1-*naphthol* was collected at 160/0·5 mm. and crystallised from

[6] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1936, **58**, 2314.
[7] Bruckner *Ber.*, 1942, **75**, 2034.

ethanol in yellow prisms (14·1 g., 37%), m. p. 165—167° (Found : C, 68·0; H, 4·3. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%). It gave an intense green colour with ferric chloride in ethanol.

3-Homopiperonylideneacetylacetone (I; R = Ac).—Homopiperonaldehyde (44 g.), acetylacetone (80 g.), pyridine (50 ml.), and piperidine (1 ml.) were heated on the steam-bath for 6 hr. The volatile material was removed under reduced pressure on the steam-bath, and the residue crystallised from ethanol. The *product* formed colourless prisms (40·7 g., 63%), m. p. 105—106°, b. p. 180°/0·1 mm. One further crystallisation from ethanol gave a specimen, m. p. 108° (Found : C, 68·0; H, 6·05. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). The substance gave a very intense but transient pure blue colour with ferric chloride in ethanol.

2-Acetyl-1-methyl-6 : 7-methylenedioxynaphthalene (III).—A solution of homopiperonylideneacetylacetone (100 mg.) in chloroform (10 ml.) was saturated at room temperature with hydrogen chloride. After 14 days it was washed with water and evaporated. *2-Acetyl-1-methyl-6 : 7-methylenedioxynaphthalene* (41 mg.), crystallised from ethanol as prisms, m. p. 134—135° (Found : C, 73·5; H, 5·3. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%), giving no colour with ferric chloride. Reaction for a shorter time sometimes gave mixtures with homopiperonylideneacetylacetone which were difficult to purify : however, warming the mixture for a few minutes with a drop of piperidine converted the diketone into a very soluble unidentified substance which was then readily removed by crystallisation.

Homoveratraldehyde.—This was prepared precisely as described for homopiperonaldehyde. The yield in the oxidation of methyleugenol to the glycol, b. p. 170/0·15 mm., was 48%; lead tetra-acetate oxidation then gave 78% of homoveratraldehyde, b. p. 130/0·3 mm., n_D^{20} 1·5469.

Ethyl 4-Acetoxy-6 : 7-dimethoxy-1-methyl-2-naphthoate (V; R = OAc).—To sodium hydride (18 g.), stirred in dry benzene (125 ml.) under nitrogen, 4-acetylveratrole (68·0 g.) and diethyl succinate (197 g.) were added slowly. The reaction soon started and continued with spontaneous refluxing for 2 hr. The mixture was then acidified with acetic acid, and benzene and water were added. Extraction of the benzene layer with sodium carbonate and acidification gave an oily acid (80·6 g.). This (15 g.) was refluxed for 5 hr. with sodium acetate (5 g.) and acetic anhydride (30 ml.), and the solution was diluted with water (500 ml.) and left overnight. The brown semisolid precipitate was filtered off and extracted with light petroleum (b. p. 60—80°) (Soxhlet). Removal of the solvent gave the yellow *ester*, which gave colourless needles (6 g.), m. p. 127°, from ethanol (Found : C, 64·7; H, 5·8. $C_{18}H_{20}O_8$ requires C, 65·0; H, 6·0%).

Ethyl 4-Hydroxy-6 : 7-dimethoxy-1-methyl-2-naphthoate (V; R = OH).—The above acetate (15 g.) was refluxed in ethanol (150 ml.) containing sodium (0·5 g.) for 4 hr., the solution was acidified with dilute hydrochloric acid, and the precipitate recrystallised from ethanol. The *phenol* (12·9 g., 96%) formed colourless needles, m. p. 205° (Found : C, 66·1; H, 6·1. $C_{16}H_{16}O_5$ requires C, 66·2; H, 6·2%). The *toluene-p-sulphonate* had m. p. 131° (Found : C, 62·1; H, 5·5. $C_{23}H_{24}O_7S$ requires C, 62·1; H, 5·4%).

Ethyl 6 : 7-Dimethoxy-1-methyl-2-naphthoate (V; R = H).—The above toluenesulphonate (7·0 g.) and Raney nickel (35 g.) in ethanol (400 ml.) were refluxed for 3 hr. The solution was filtered and concentrated to small volume; crystals separated and on crystallisation from benzene gave the phenol (1·3 g.), m. p. and mixed m. p. 206°. Extraction of the residue from the mother-liquor with hot light petroleum (b. p. 60—80°), cooling (crystals; 3·2 g.; m. p. 85—97°), sublimation at 120°/0·03 mm., and recrystallisation from light petroleum gave *ethyl 6 : 7-dimethoxy-1-methyl-2-naphthoate* as colourless plates (1·1 g.), m. p. 108—109° (Found : C, 70·3; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%).

2-Acetyl-6 : 7-dimethoxy-1-methylnaphthalene (VI).—*Method A.* The preceding naphthoate (200 mg.) was hydrolysed with sodium hydroxide to the *acid* (163 mg., 91%), m. p. 276° (Found : C, 68·1; H, 5·9. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%), which (57·2 mg.) with phosphorus pentachloride (60 mg.) in hot toluene (10 ml.) on the steam-bath for 0·5 hr. gave the solid acid chloride. This was refluxed with dimethylcadmium [from magnesium (100 mg.), methyl bromide (400 mg.), and cadmium chloride (500 mg.)] in benzene (10 ml.) for 0·5 hr. Dilute sulphuric acid and ether were added and the organic layer was worked up in the usual way. *2-Acetyl-6 : 7-dimethoxy-1-methylnaphthalene* formed plates (33 mg.), m. p. 161°, from ethanol (Found : C, 73·1; H, 6·3. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

γ-(2-Acetyl-4 : 5-dimethoxyphenyl)butyric Acid.—Ethyl γ-3 : 4-dimethoxyphenylbutyrate (32·5 g.) in methylene chloride (40 ml.) was added to aluminium chloride (12 g.) in nitrobenzene (40 ml.) containing acetyl chloride (6 ml.) and kept overnight. The solution was added to ice and hydrochloric acid, the organic layer washed with aqueous sodium hydroxide and water and evaporated, and the residue distilled. The distillate (32 g.), b. p. 188/0·5 mm., was hydrolysed with aqueous sodium hydroxide to the *acid* (20 g., 58%), m. p. 88—89° (from toluene)

(Found : C, 62·7; H, 6·5. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). The *semicarbazone* of the ethyl ester had m. p. 167—168° (from ethanol) (Found : C, 58·3; H, 7·0; N, 12·4. $C_{17}H_{25}O_5N_3$ requires C, 58·2; H, 7·1; N, 12·0%).

5-(2-Acetyl-4 : 5-dimethoxyphenyl)pentan-2-one (VII; R = Me).—γ-(2-Acetyl-4 : 5-dimethoxyphenyl)butyric acid (27 g.) was kept overnight in toluene (175 ml.) with phosphorus pentachloride (22 g.). The toluene was then evaporated on the steam-bath at 15 mm. and the residue added in benzene (30 ml.) to a solution of dimethylcadmium [from magnesium (4·9 g.), excess of methyl bromide, and cadmium chloride (19·6 g.) in ether (100 ml.)] in benzene (120 ml.). After the initial vigorous reaction the solution was refluxed for 1 hr., then poured on ice and dilute hydrochloric acid, and the organic layer worked up in the usual way. From the alkaline washings was obtained recovered acid (2·2 g.). The neutral product (24·5 g.), crystallised from light petroleum (b. p. 80—100°), gave *5-(2-acetyl-4 : 5-dimethoxyphenyl)pentan-2-one* (8 g.) as yellow prisms, m. p. 88° (Found : C, 68·4; H, 7·55. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

2-Acetyl-3 : 4-dihydro-6 : 7-dimethoxy-1-methylnaphthalene (VIII).—The foregoing pentanone (5 g.) was heated in ethanol (20 ml.) containing sodium (0·4 g.) for 1 hr. Next morning *2-acetyl-3 : 4-dihydro-6 : 7-dimethoxy-1-methylnaphthalene* (4·2 g.) was filtered off and recrystallised from ethanol as yellow plates, m. p. 109° (Found : C, 73·4; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

In a similar way the mother-liquors from the preparation of the diketone were cyclised, to yield a total of 15·5 g. of pure cyclised ketone from the 27 g. of acid.

2-Acetyl-6 : 7-dimethoxy-1-methylnaphthalene.—Method B. (*a*) The dihydro-ketone (1·0 g.) and sulphur (0·121 g.) were heated at 230° for 15 min. and then at 250° for 15 min. The product, crystallised from benzene and then ethanol, yielded 2-acetyl-6 : 7-dimethoxy-1-methylnaphthalene (0·7 g.) as reddish-brown crystals, m. p. 162° alone or mixed with the previous sample (Found : C, 73·8; H, 6·6%), but could not be obtained colourless.

(*b*) The dihydro-ketone (5 g.) and 10% palladised charcoal (0·2 g.) were refluxed for 5 hr. in toluene (50 ml.). The product crystallised as colourless plates, m. p. 161° (2·3 g.).

Diethyl 3 : 4-Dihydro-6 : 7-dimethoxynaphthalene-1 : 2-dicarboxylate.—Ethanol (16 ml.) was added to powdered potassium (10·4 g.) under ether (150 ml.) and the mixture kept overnight. Ethyl oxalate (53 ml.) was then added, and after ½ hr. ethyl γ-3 : 4-dimethoxyphenylbutyrate (67 g.). The mixture was refluxed for 2 hr., then cooled in ice and decomposed with ice–water. The aqueous layer was acidified with sulphuric acid and the liberated red oil extracted with ether. After the removal of volatile matter on the steam-bath, the residue was stirred at 0° into syrupy phosphoric acid (220 ml.) and concentrated sulphuric acid (46 ml.) and the deep red solution kept for 1 hr. at room temperature, then poured into ice water (3 l.). An oil which separated rapidly crystallised. Recrystallisation from acetone gave *diethyl 3 : 4-dihydro-6 : 7-dimethoxynaphthalene-1 : 2-dicarboxylate* (38 g., 42%) as bright yellow tablets, m. p. 104—105° (Found : C, 64·5; H, 6·8. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%).

Hydrolysis of the diethyl ester with potassium hydroxide gave the dicarboxylic acid as pale yellow needles which reddened and then melted at 187—188° as it was converted into the anhydride. The anhydride, which was more conveniently prepared by heating the acid with acetic anhydride, crystallised from benzene as scarlet needles, m. p. 188° (Found : C, 64·3; H, 4·8. Calc. for $C_{14}H_{12}O_5$: C, 64·6; H, 4·6%). On boiling with aqueous alkali, the acid was recovered.

Diethyl 6 : 7-Dimethoxynaphthalene-1 : 2-dicarboxylate.—The 3 : 4-dihydro-ester (2·6 g.) and sulphur (0·32 g.) were heated to 235° for 20 min. and then at 250° for 30 min. The product was sublimed at 300° in a vacuum and crystallised from light petroleum (b. p. 60—80°). *Diethyl 6 : 7-dimethoxynaphthalene-1 : 2-dicarboxylate* formed pale yellow prisms (1·1 g.), m. p. 91—92° (Found : C, 64·9; H, 6·1. $C_{18}H_{20}O_6$ requires C, 65·06; H, 6·0%).

The acid, produced by hydrolysis with potassium hydroxide, formed nearly colourless needles (from water), which became yellow and melted at 233°. The anhydride, prepared with acetic anhydride, formed yellow prisms, m. p. 233°, from benzene (Found : C, 65·3; H, 4·3. Calc. for $C_{14}H_{10}O_5$: C, 65·1; H, 3·9%).

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818. *Aromatic Substitution. Part II.* Nitration of Aromatic Compounds with Nitronium Tetrafluoroborate and Other Stable Nitronium Salts.*

By G. Oláh, S. Kuhn, and A. Mlinkó.

A new method of nitration of aromatic compounds has been developed by use of stable nitronium salts, first, with nitronium tetrafluoroborate.

Moissan and Lebeau,[1] using material which probably contained some nitryl fluoride,[2] obtained evidence of formation of nitrobenzene from benzene. Using pure nitryl fluoride, now readily prepared, Hetherington and Robinson[3] have surveyed its nitrating properties towards organic compounds, alone or dissolved in an inert liquid. Of the organic compounds used some were inert (aliphatic hydrocarbons and deactivated aromatic compounds such as nitrobenzene), some were nitrated normally, and some were destroyed (*e.g.*, aniline, which rapidly gave tars). As expected, those undergoing nitration gave the same nitro-compounds as result from the use of mixed acids. Hetherington and Robinson postulated that the nitration is due to the nitronium ion NO_2^+, formed by dissociation of the nitryl fluoride in the liquid undergoing treatment. During investigation of the mechanism of nitration Goddard, Hughes, and Ingold[4] isolated some nitronium salts, $[NO_2^+]X^-$, *e.g.*, the perchlorate, hydrogen disulphate, neutral disulphate, neutral nitronium trisulphate, and fluorosulphonate. The ionic constitutions assigned were spectroscopically established. The compounds isolated were not sufficiently stable for use as nitrating agents and as yet nothing has been published about the kinetics of reaction of these compounds. Woolf and Emeléus[5] treated oxy-salts with bromine trifluoride and nitrogen oxide, and so obtained a number of nitronium salts, such as the tetrafluoroborate, hexafluorostannate, hexafluorophosphate, hexafluoroarsenate, hexafluoroantimonate, and tetrafluoroaurate, but did not refer to their use as nitrating agents. So nothing has been known hitherto about the use of stable nitronium salts as nitrating agents.

We have found that some nitronium salts, first, nitronium tetrafluoroborate,[6] and then the hexafluorosilicate, hexafluoroantimonate, and hexafluorophosphate, are useful nitrating agents.

Of the stable nitronium salts it seems that the tetrafluoroborate is the most convenient. It can be prepared by Aynsley, Hetherington, and Robinson's method[2] from nitryl fluoride and boron trifluoride, or without the use of elementary fluorine by Schmeisser and Elischer's method,[7] by the reaction of dinitrogen pentoxide with hydrogen fluoride and boron trifluoride in nitromethane. Nitronium tetrafluoroborate, which is a white crystalline compound, is stable in the absence of moisture and is adaptable as a nitrating agent for common use. For instance, with it we have nitrated the compounds listed in the Table, with the yields stated. For the experimental methods see the Experimental section. In the case of nitrogen-containing compounds such as diethyl- and dimethyl-aniline or pyridine the basic nitrogen atom reacts first with the nitronium salt, and isolation of nitrated compounds is complicated.

Nitronium hexafluorosilicate, hexafluoroantimonate, and hexafluorophosphate behave similarly as nitrating agents (see Table), but because of the greater difficulty of preparing them are less important.

Nitration with nitronium tetrafluoroborate follows the general scheme :

$$ArH + NO_2^+BF_4^- \longrightarrow Ar{\cdot}NO_2 + HF + BF_3$$

* Part I, *Chem. Ber.*, 1956, **89**, 866.

[1] Moissan and Lebeau, *Compt. rend.*, 1905, **140**, 1573, 1621.
[2] Aynsley, Hetherington, and Robinson, *J.*, 1954, 1119.
[3] Hetherington and Robinson, *J.*, 1954, 3512.
[4] Goddard, Hughes, and Ingold, *J.*, 1950, 2559.
[5] Woolf and Emeléus, *J.*, 1950, 1050.
[6] Oláh and Kuhn, *Chem. and Ind.*, 1956, 98.
[7] Schmeisser and Elischer, *Z. Naturforsch.*, 1952, **7b**, 583; G. P. 918,506/1955.

The salt-like character of nitronium tetrafluoroborate was proved by our electric conductivity measurements. Nitronium tetrafluoroborate has a specific conductivity (κ) in 0·02% nitromethane solution of $0{\cdot}75 \times 10^{-4}\ \Omega^{-1}$ cm.$^{-1}$; the solvent, nitromethane, has $\kappa = 3{\cdot}18 \times 10^{-6}\ \Omega^{-1}$ cm.$^{-1}$; thus the specific conductivity of the pure electrolyte is $0{\cdot}72 \times 10^{-4}\ \Omega^{-1}$cm.$^{-1}$. In 0·2% solution, nitronium fluoroborate has $\kappa = 6{\cdot}3 \times 10^{-4}\ \Omega^{-1}$ cm.$^{-1}$; the pure electrolyte has $0{\cdot}68 \times 10^{-3}\ \Omega^{-1}$ cm.$^{-1}$.

Compound nitrated	Yield (%) of mononitro-product	Method
By use of NO_2BF_4		
Benzene	87	A
Toluene	88	A
Nitrobenzene	85·5	B
Fluorobenzene	82	A
Chlorobenzene	77	A
Bromobenzene	90·5	A
Iodobenzene	88	A
o-Dichlorobenzene	91·5	A
Naphthalene	93	C
Anthracene	98	C
Thiophen	91·5	C
Furan	14 *	C
By use of $(NO_2)_2SiF_6$		
Benzene	93	A
Nitrobenzene	82	B
By use of NO_2SbF_6		
Benzene	84	A
By use of NO_2PF_6		
Benzene	90	A

* With much decomp.

The new nitration by the stable nitronium salts gives a direct preparative proof of the electrophilic character of nitration through the NO_2^+ cation. It also made it possible to examine the kinetics of nitration in very advantageous circumstances: results of the kinetic investigations will be reported later.

Experimental

Nitronium Tetrafluoroborate (cf. Schmeisser and Elischer [7]).—To a solution of dinitrogen pentoxide (108 g., 1 mole) in nitromethane (150 g.) at −20° is added anhydrous hydrogen fluoride (20 g., 1·0 mole). The solution is then saturated with boron trifluoride. Nitronium tetrafluoroborate separates and is collected and dried *in vacuo* over phosphoric oxide (yield, 125 g., 94%) (Found: F, 56·8; N, 10·5. Calc. for O_2NF_4B: F, 57·1; N, 10·5%). The salt is stable in absence of moisture but is hygroscopic (with subsequent decomposition) and when heated decomposes at *ca.* 170° without melting or subliming.

Nitronium Hexafluorosilicate (cf. Schmeisser and Elischer [7]).—Replacing the boron trifluoride in the above preparation by silicon fluoride (52 g., 0·5 mole) gives the hexafluorosilicate (107·6 g., 92%) (Found: F, 48·3; N, 12·2; Si, 11·7. Calc. for $O_4N_2F_6Si$: F, 48·7; N, 12·0; Si, 12·0%).

Nitronium hexafluoroantimonate (Found: F, 39·9; N, 5·2; Sb, 42·6. Calc. for O_2NF_6Sb: F, 40·4; N, 5·0; Sb, 43·2%) and hexafluorophosphate (Found: F, 59·3; N, 7·1; P, 16·0. Calc. for O_2NF_6P: F, 59·7; N, 7·3; P, 16·2%) were prepared as described by Woolf and Emeléus.[8]

Nitrations.—Method A. To 0·2 mole of the dry aromatic compound was added, in small portions with ice–salt cooling and stirring, 0·1 mole of the nitronium salt. A very exothermic reaction took place. Then the mixture was allowed to warm to room temperature and kept for some hours. The mixture was washed free from acid, dried ($CaCl_2$), and distilled.

Method B. In the case of deactivated aromatic rings the reaction was effected at 20—130°.

Method C. For solid or highly sensitive ring systems, the reaction was effected in 5—10% ether solution.

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819. *The Chemistry of Gum Labdanum. Part I. Some Acidic Constituents.*

By J. D. Cocker, T. G. Halsall, and (in part) A. Bowers.

The acid fraction from gum labdanum has been examined. *p*-Anisic acid, β-phenylpropionic acid, and two new diterpene acids have been isolated, in addition to straight-chain fatty acids and long-chain hydroxy-acids. One of the diterpenes, labdanolic acid, is a bicyclic hydroxy-acid, $C_{20}H_{34}O_3$. The other is a bicyclic compound, $C_{20}H_{32}O_3$, which contains an αβ-unsaturated ketone grouping.

Spanish gum labdanum, which is obtained from *Cistus ladaniferus* ("rock-rose") [1] by boiling the wood of the bramble in water and collecting the resin from the surface,[2,3,4,5] has been little investigated in the past. It is dark brown to black and sold as pitch-like blocks. Considerable quantities are produced in Spain (50 tons a year [6]) and it is used as a fixative in perfumery. Hence the use also of names "black amber" and "black balsam." The gum consists mainly of water, resin, and impurities such as earth [6] and contains only little volatile oil (1—2%). The few past investigations have been concerned with the characteristics of this oil [7,8] and even here very little work of a truly chemical nature has apparently been carried out. Probably the most important is that of Masson [8] who isolated acetophenone and 2 : 2 : 6-trimethyl*cyclo*hexanone. We have commenced an investigation of a commercial sample of the gum and in this paper describe the isolation of some of its acidic constituents.

The gum, which contained 1·6% of steam-volatile material, was only partially soluble in light petroleum, giving an almost colourless extract from which a crystalline saturated paraffin, m. p. 63—64°, was obtained by chromatography. The melting point and analytical data suggest that this is very similar to that of the broom-wax paraffin, m. p. 64—65°, isolated by Musgrave, Stark, and Spring,[9] who suggest that their material is a mixture of approximately 60% of *n*-nonacosane and 40% of *n*-hentriacontane.

Most of the gum was soluble in ether, and the ether-soluble material was separated into acidic, phenolic (and acidic), and neutral fractions by extraction with potassium hydrogen carbonate solution and sodium carbonate solution. The examination of the phenolic and the neutral fractions is not yet complete.

The acidic portion was esterified with ethereal diazomethane and the resulting methyl esters were taken up in light petroleum and separated by chromatography into five broad fractions (*A*, 10%; *B*, 25%; *C*, 25%; *D*, 13%; and *E*, 20%) of increasing polarity.

The infrared spectrum of fraction *A* in "Nujol" was typical of that of the methyl esters of straight-chain saturated fatty acids, *e.g.*, it showed the typical band progression [10] between 1180 and 1295 cm.$^{-1}$. By repeated crystallisation crystals, m. p. 43—44°, were obtained with analytical figures best in agreement with the formula $C_{22}H_{44}O_2$ or $C_{23}H_{46}O_2$. The latter corresponds to methyl docosanoate. The melting point, however, is best in agreement with that (m. p. 46—47°) [11] of the methyl ester of the lower homologue, methyl eicosanoate. It is probable that the substance obtained from gum labdanum is a mixture of the methyl esters of these two acids.

Fraction *B* was separated by chromatography into a number of fractions, which formed three groups. Hydrolysing each group with aqueous methanolic potassium hydroxide gave

[1] Montero, *Ion*, 1951, **12**, 565 (*Chem. Abs.*, 1952, **46**, 6331).
[2] Howes, "Vegetable Gums and Resins," Chronica Botanica Co., Waltham, Mass., 1949, p. 158.
[3] Howes, *Econ. Bot.*, 1950, **4**, 307.
[4] Geradin, *Bull. Sci. pharmacol.*, 1919, **26**, 289 (*Chem. Abs.*, 1919, **13**, 2104).
[5] Igolen, *Parfums France*, 1937, **15**, 164 (*Chem. Abs.*, 1937, **31**, 7602).
[6] Paltre, *Ion*, 1952, **12**, 132 (*Chem. Abs.*, 1952, **46**, 10546); see also Emmanuel, *Arch. Pharm.*, 1912, **250**, 111.
[7] Anon, *Roure-Bertrand Fils, Sci. Ind. Bull.*, [4], 1920, No. 2, p. 25 (*Chem. Abs.*, 1921, **15**, 2149).
[8] Masson, *Compt. rend.*, 1912, **154**, 517.
[9] Musgrave, Stark, and Spring, *J.*, 1952, 4393.
[10] Jones, McKay, and Sinclair, *J. Amer. Chem. Soc.*, 1952, **74**, 2575.
[11] Adams and Dyer, *J.*, 1925, **127**, 70.

dihydrocinnamic acid, *p*-anisic acid, and a new acid, $C_{20}H_{32}O_3$. The infrared spectrum of the last acid had a band at 1668 cm.$^{-1}$ indicative of an αβ-unsaturated ketone grouping. This was confirmed by its ultraviolet absorption spectrum with a maximum at 2385 Å (ε 11,470). After allowance for one double bond and two carbonyl groups the formula of this new unsaturated keto-acid indicates that it is bicyclic. In view of the isolation also of a bicylic diterpene hydroxy-acid (see below) it is probable that the acid is a diterpene. If so, it is the first diterpene containing an αβ-unsaturated ketone grouping to be isolated. From the ultraviolet data the double bond of the αβ-unsaturated system must have two alkyl substituents.

Fraction *C* was mainly composed of the methyl ester of a new hydroxy-acid, $C_{20}H_{36}O_3$, named labdanolic acid. The infrared spectrum showed the presence of methoxycarbonyl and hydroxyl groups and gave no indication of the presence of a double bond. Hydrolysis gave the free acid which was characterised as its *cyclo*hexylamine salt. The equivalent weight confirmed the formula $C_{20}H_{36}O_3$ which, after allowance for the carbonyl group, indicated that labdanolic acid was bicyclic. The presence of twenty carbon atoms suggested that it was a diterpene. This is shown to be correct in the following paper.

The infrared spectra of fractions *D* and *E* suggest that they are composed of long-chain hydroxy-acids. They have not been examined in detail.

So far no evidence of the presence of triterpenes in gum labdanum has been obtained. In Nature triterpenes and diterpenes do not appear to be found together and the results with gum labdanum are in line with this. Triterpenes and steroids have oxygen at $C_{(3)}$ and are formed by the cyclisation of squalene initiated by an oxidative electrophilic reagent.[12] Diterpenes, on the other hand, have no oxygen at $C_{(3)}$* and their formation appears to be initiated in quite a different manner. It may well be that the enzyme systems leading to steroids and triterpenes on the one hand and to diterpenes on the other are incompatible.

Experimental

Rotations were determined for $CHCl_3$ solutions at room temperature. M. p.s were determined on a Kofler block and are corrected. The alumina used for chromatography had an activity I—II unless otherwise stated. Light petroleum refers to the fraction with b. p. 60—80°. Unless otherwise stated infrared data refer to carbon disulphide solution.

Steam-distillation of Gum Labdanum.—Gum labdanum (135 g.) was steam-distilled until 4 l. of distillate had been collected. Ether-extraction of the distillate yielded a pleasant-smelling oil (2·0 g.), distillation of which gave fractions (each 300 mg.), b. p. 125—130° (bath-temp.)/14 mm., n_D^{18} 1·4838, and b. p. 135—150° (bath-temp.)/14 mm., n_D^{18} 1·4933. The residue was non-volatile.

Extraction of Gum Labdanum with Light Petroleum.—The gum (60 g.), a plastic material at room temperature, became brittle at 0°. It was powdered and treated with light petroleum (b. p. 40—60°; 400 c.c.) for 2 days with occasional shaking. After filtration, evaporation afforded a pale yellow gum (6·8 g.) which was absorbed from light petroleum (40 c.c.) on alumina (200 g.). Elution with light petroleum yielded a crystalline fraction (0·75 g.), m. p. 59—63°. Crystallisation of this material from ethyl acetate afforded a saturated paraffin as plates, m. p. 63—64° (Found : C, 85·4, 85·2; H, 14·8, 14·9. Calc. for $C_{29}H_{60}$: C, 85·2; H, 14·8. Calc. for $C_{31}H_{64}$: C, 85·25; H, 14·75%). Continued elution of the column with solvents of increasing polarity yielded only intractable gums.

Separation of the Acidic Fraction of Gum Labdanum.—Gum labdanum (4 kg.) was taken up in ether (10 l.) and the insoluble material, which causes formation of emulsions during the extractions, was removed by centrifugation. The black ether solution was then washed with potassium hydrogen carbonate solution until the washings were colourless. The total extract was then acidified to pH 5 with 50% aqueous acetic acid, and the liberated acids (X) were taken up in ether. Removal of the ether under reduced pressure gave the crude acids (1 kg.) as a viscous black tar. Further extraction of the ethereal solution of the gum with sodium hydroxide

* The numbering system used is the same as that used for triterpenes and steroids (see following paper).

[12] Tchen and Bloch, *J. Amer. Chem. Soc.*, 1956, **78**, 1516, and the refs. cited therein.

solution gave a phenolic fraction (2·2 kg.). The extracted ether solution was then pale yellow and was evaporated to give the neutral fraction as a pale yellow solid (700 g.).

The acids (X) were dissolved in ether (1 l.) and methanol (1 l.) and treated with an ethereal solution of diazomethane until evolution of nitrogen ceased. The solution of methyl esters was then washed twice with ice-cold N-potassium hydroxide (500 c.c.) and once with saturated brine. After removal of the solvents the esters were extracted with boiling light petroleum (1 l.) three times. The combined extracts were made up to a total volume of 8 l. with light petroleum and kept overnight. The solution was then decanted from the precipitated tar and evaporated under reduced pressure to give a clear red viscous syrup (760 g.). This was chromatographed in 150 g. portions, being adsorbed from light petroleum on alumina (3 kg.) which had been deactivated with 3% of 10% acetic acid. The column was eluted as follows: light petroleum (1 l.) gave fraction *A* (15 g.); light petroleum–benzene (3 : 1; 6 l.) gave fraction *B* (*ca.* 40 g.); benzene (19 l.) gave fraction *C* (*ca.* 40 g.); ether (5 l.) gave fraction *D* (*ca.* 20 g.); and methanol (3 l.) gave fraction *E* (*ca.* 30 g.).

Fraction A. This consisted of the methyl esters of normal long-chain acids. The infrared spectrum was typical of such esters. Infrared absorption (melt): bands at 717 and 728 (split), 1466, 1476, and 1747 cm.$^{-1}$. Repeated crystallisation from chloroform–methanol gave plates, m. p. 43—44° (Found: C, 77·95, 77·85; H, 12·95, 13·05. Calc. for $C_{23}H_{46}O_2$: C, 77·9; H, 13·1. Calc. for $C_{21}H_{42}O_2$: C, 77·25; H, 12·95%).

Fraction B. A portion of fraction *B* (14 g.) was adsorbed from light petroleum on alumina (600 g.) which had been deactivated with 10% aqueous acetic acid (18 c.c.). Elution with the solvent as indicated gave fractions: (*a*) With 200 c.c. portions of light petroleum: (1) nil, (2) 0·04 g., (3) 0·02 g., (4) 0·07 g., (5) 0·66 g., (6) 0·61 g., (7) 0·41 g., (8) 0·28 g., (9) 0·23 g., (10) 0·27 g., (11) 0·17 g., (12) 0·16 g., (13) 0·16 g., n_D^{15} 1·4932. (*b*) With 400 c.c. portions of light petroleum: (14) 0·28 g., (15) 0·26 g., n_D^{15} 1·4970, (16) 0·22 g., n_D^{15} 1·4970, (17) 0·17 g., (18) 0·14 g., n_D^{15} 1·4990, (19) 0·13 g., (20) 0·12 g. (*c*) With 400 c.c. portions of light petroleum–benzene (4 : 1): (21) 0·20 g., (22) 0·14 g., (23) 0·12 g. (*d*) With 400 c.c. portions of light petroleum–benzene (2 : 1): (25) 0·02 g., (26) 0·50 g., n_D^{15} 1·4942, (27) 0·65 g., (28) 0·62 g., (29) 0·51 g., (30) 0·45 g., (31) 0·36 g. (*e*) With 400 c.c. portions of light petroleum–benzene (1 : 1): (32) 0·54 g., (33) 0·40 g., (34) 0·55 g. (*f*) With 400 c.c. portions of benzene: (35) 0·82 g., (36) 0·37 g., (37) 0·23 g., (38) 0·18 g. (*g*) With 400 c.c. benzene–ether (20 : 1): (39) 0·54 g.

From their infrared spectra and refractive indices fractions (14)—(21) appeared to be identical and homogeneous. Hydrolysis of them with aqueous-methanolic potassium hydroxide gave β-phenylpropionic acid, m. p. 42—46°, which from light petroleum (b. p. 40—60°) afforded needles, m. p. and mixed m. p. 48—49° (Found: C, 71·65; H, 6·4. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%). The infrared spectrum was identical with that of an authentic sample.

Fractions (22)—(27) appeared to be identical and homogeneous and were hydrolysed with aqueous-methanolic potassium hydroxide to *p*-anisic acid, m. p. 176—183°, which on repeated crystallisation from aqueous methanol formed needles, m. p. and mixed m. p. 177—184° with a change in crystalline shape at 117° (Found: C, 63·25; H, 5·2. Calc. for $C_8H_8O_3$: C, 63·15; H, 5·3%). The infrared spectrum was identical with that of *p*-anisic acid.

Fractions (28)—(35) appeared to be identical and homogeneous and were hydrolysed with aqueous-methanolic potassium hydroxide to give an *acid*, m. p. 94—110°. Crystallisation from methanol–water (6 : 4) gave prisms (2·0 g.), m. p. 114—115°, $[\alpha]_D$ +13·5° (*c*, 1·7) (Found: C, 74·85, 74·95; H, 10·1, 10·2. $C_{20}H_{32}O_3$ requires C, 74·95; H, 10·05%). Light absorption max. in EtOH at 2385 Å (ε 11,470). Infrared absorption bands at 1668 and 1703 cm.$^{-1}$.

Fraction C. Fraction *C* (40 g.) when kept became semisolid and on repeated recrystallisation from light petroleum (b. p. 40—60°) (cooling to −5°) gave *methyl labdanolate* (24 g.), white needles, m. p. 73—74°, $[\alpha]_D$ −8·0° (*c*, 2·0) (Found: C, 74·35, 74·35; H, 11·3, 11·4%; sap. val., 336, 340. $C_{21}H_{38}O_3$ requires C, 74·5; H, 11·3%; sap. val., 338·5). Infrared absorption bands at 1365, 1386, 1738, and 3560 cm.$^{-1}$.

Fractions D *and* E. A preliminary examination of the infrared spectra of these fractions (bands at 1738 and 3480 cm.$^{-1}$) suggested that they were mainly composed of the methyl esters of long-chain hydroxy-acids.

Labdanolic Acid (8α-*Hydroxylabdan*-15-*oic Acid*).—Methyl labdanolate (630 mg.) was hydrolysed under reflux for 1 hr. with a solution from sodium (410 mg.) in ethanol (12 c.c.) and water (0·2 c.c.). The resulting *acid* was a gum, $[\alpha]_D$ −7° (*c*, 0·98) (Found: C, 73·5; H, 11·15. $C_{20}H_{34}O_3$ requires C, 74·0; H, 11·2%). The acid (580 mg.) was treated in hot ethyl acetate (5 c.c.) with *cyclo*hexylamine (0·3 c.c.). On cooling the cyclo*hexylamine salt* separated. When crystallised from ethyl acetate to constant rotation it formed needles, m. p. 115—135° (dependent upon the

rate of heating), $[\alpha]_D$ −12° (*c*, 1·4) (Found: C, 73·5; H, 11·65; N, 3·5. $C_{26}H_{49}O_3N$ requires C, 73·7; H, 11·65; N, 3·3%).

The authors thank Professor E. R. H. Jones, F.R.S., for his interest. One of them (J. D. C.) thanks the Department of Scientific and Industrial Research for a maintenance grant and another (A. B.) the Ministry of Education for the award of a Technical State Scholarship. Some of the infrared spectra were determined under the direction of Dr. G. D. Meakins and the remainder by Mr. F. Hastings under the supervision of Dr. F. B. Strauss.

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820. *The Chemistry of Gum Labdanum. Part II.*[1] *The Structure of Labdanolic Acid.*

By J. D. COCKER and T. G. HALSALL.

The structure of labdanolic acid, a constituent of gum labdanum, has been shown to be (I).

IN Part I [1] the isolation was described of labdanolic acid, a new bicyclic diterpene hydroxy-acid, $C_{20}H_{36}O_3$. It has now been shown to have structure (I).*

Labdanolic acid was obtained by relatively mild hydrolysis of its methyl ester, showing that its carboxyl group was unhindered and not situated in the sterically hindered 4-position as in the majority of diterpene acids. The hydroxyl group, on the other hand, was unreactive, being acetylated only under vigorous conditions. On attempted mild oxidation of methyl labdanolate with chromic acid the ester was recovered unchanged. Reduction of the ester with lithium aluminium hydride gave the diol (III) which on mild acetylation afforded a monoacetate. The hydroxyl group was accordingly tertiary.

Dehydration of methyl labdanolate with phosphoryl chloride in pyridine gave a homogeneous product (IV), the infrared spectrum of which indicated the presence of a vinylidene group (bands at 890 and 1645 cm.$^{-1}$). This was confirmed by ozonolysis, formaldehyde and a keto-ester (V) being obtained. Reduction of the dehydration product, which was also formed when methyl labdanolate was acetylated under vigorous conditions, gave the alcohol (VI). This was characterised by conversion with osmium tetroxide in pyridine into a triol which is provisionally formulated as (VII), addition being assumed on the less hindered (α) side of the molecule (see below, however).

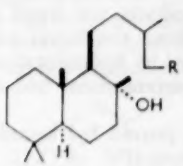
The keto-ester (V) formed an oxime but not a 2 : 4-dinitrophenylhydrazone. These observations together with the carbonyl bands in the infrared spectrum at 1735 cm.$^{-1}$ (ester band) and 1712 cm.$^{-1}$ (aliphatic or 6-membered ring ketone band) suggested that the keto-ester contained a somewhat hindered keto-group in a six-membered ring. The formation of a hindered keto-group in a side chain appeared unlikely as it could only be accounted for by a branched side chain unlike any found in bicyclic diterpenes. In turn, methyl labdanolate must have contained the grouping (VIII), with the hydroxyl group in the equatorial conformation to account for the formation of an exocyclic rather than an endocyclic double bond on dehydration.

Dehydrogenation of the unsaturated alcohol (VI) with a platinum–charcoal catalyst gave a trimethylnaphthalene. It was identified as the 1 : 2 : 5-trimethyl isomer by comparison of its ultraviolet absorption spectrum with the spectra of the trimethylnaphthalenes described by Heilbronner, Fröhlicher, and Plattner [2] and by formation of the 1 : 3 : 5-trinitrobenzene adduct. In addition 1 : 2 : 5 : 6-tetramethylnaphthalene was obtained and characterised as its 1 : 3 : 5-trinitrobenzene adduct.

* The nomenclature used in this paper is based on the parent hydrocarbon (II) which is provisionally called labdane and, on the advice of the Editor, is numbered on the principles used for steroids. This hydrocarbon was previously called agathane and numbered differently. It is to avoid confusion in numbering that a new name is suggested.

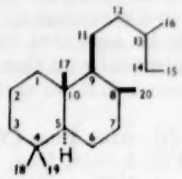
[1] Part I, Cocker, Halsall, and Bowers, preceding paper.
[2] Heilbronner, Fröhlicher, and Plattner, *Helv. Chim. Acta*, 1949, **32**, 2479.

The isolation of 1 : 2 : 5-trimethyl- and 1 : 2 : 5 : 6-tetramethyl-naphthalene suggested that labdanolic acid was related to the group of bicyclic diterpenes typified by sclareol (IX) * [3,4] and manoöl (X) * [3,4] and that its structure was either (I) (or a stereoisomer) or (XI). The former possibility led to structure (IV) (or a stereoisomer) for the dehydration product from methyl labdanolate. During the course of our work on labdanolic acid King

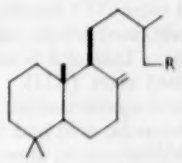


(I) R = CO_2H

(III) R = CH_2·OH

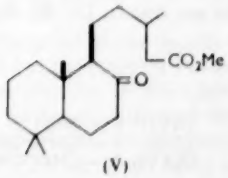


(II)

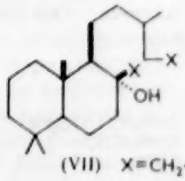


(IV) R = CO_2Me

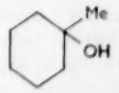
(VI) R = CH_2·OH



(V)



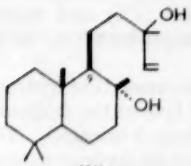
(VII) X = CH_2·OH



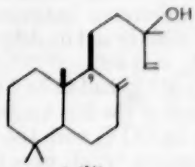
(VIII)

and Jones [5] showed that the methyl ester of eperuic acid, a new bicyclic diterpene from wallaba oleo-resin, was a stereoisomer of (IV). Comparison, however, of the rotation of methyl eperuate with that of the unsaturated ester (IV) from methyl labdanolate indicated that they were not identical (see below).

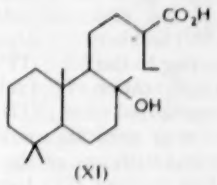
Treatment of the unsaturated ester (IV) with acid gave an isomer, the infrared spectrum



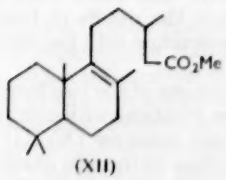
(IX)



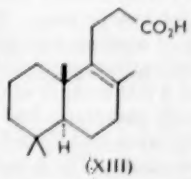
(X)



(XI)



(XII)



(XIII)

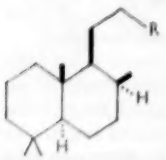
of which did not show any bands indicative of a trisubstituted double bond or a vinylidene group. The isomer had accordingly a tetrasubstituted double bond and it was formulated as (XII). Support for this conclusion was obtained on hydrogenating the isomer. Only one product was obtained and the change in molecular rotation (−112°) was very similar

* The configuration of $C_{(9)}$ in manoöl and sclareol has not been rigorously proved (cf. ref. 4).

[3] Barton, *Quart. Rev.*, 1949, **3**, 36.
[4] Klyne, *J.*, 1953, 3072.
[5] King and Jones, *J.*, 1955, 658.

to that (−136°) found when the acid (XIII) is hydrogenated.[6,7] The stereochemistry of the hydrogenation product is discussed below. Treatment of the isomer with osmium tetroxide in pyridine gave the glycol. The stereochemistry of the addition is uncertain. Addition from the less hindered (α) side would be expected, but Dietrich, Lederer, and Mercier [6] have described results which indicate that when the closely related compound (XIII) is similarly oxidised the product of β-addition is formed. When the original unsaturated ester (IV) was hydrogenated a mixture of two products, one liquid and one solid, was obtained which could only be separated by absorbing the liquid isomer on porous plates. The solid isomer was identical with that obtained by hydrogenation of the acid-isomerised ester (XII). This proved that no skeletal rearrangement had occurred during the acid-isomerisation.

That labdanolic acid had formula (I) rather than (XI) was proved by degradation of the solid hydrogenation product (XIV), formed from the esters (IV) or (XII), by the Barbier–Wieland technique to the acid (XV) and thence to the methyl ketone (XVI). Hypoiodite oxidation of this gave an acid, m. p. 141—143°, $[\alpha]_D$ +40°, which was shown to be identical (mixed m. p. and identical infrared spectra) with the acid (XVII) obtained by Burn and Rigby [7] starting from marrubiin and which was shown by these authors to be identical with material derived from ambrein. Our thanks are due to Dr. W. Rigby for supplying us with a sample of this acid.



(XIV) R = CHMe·CH_2·CO_2Me
(XV) R = CHMe·CO_2H
(XVI) R = COMe

(XVII) R = CO_2H
(XXV) R = CHMe·CH=CPh_2
(XXVI) R = CMe=CPh_2

The identity of the C_{17} acid from labdanolic acid with that from marrubiin and ambrein proved that the rings in labdanolic acid were *trans*-fused and that the absolute configuration at $C_{(10)}$ was the same as in ambrein and in the di- and tri-terpenes. In turn it followed that the 8-hydroxyl group, which had been shown to be equatorial, was in the α- and the 8-methyl group in the β-configuration. These configurations were confirmed by comparison of the molecular-rotation differences between sclareol (IX) and manoöl (X) (ΔM_D +98°) and between labdanolic acid (I) and its dehydration product [*i.e.*, the free acid corresponding to the ester (IV)] (ΔM_D = +99°).

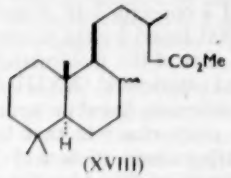
The configuration of the side chain at $C_{(9)}$ had to be β if one assumed that hydrogenation of the unsaturated ester (XII) occurred at the less hindered (α) face of the molecule. The saturated ester resulting would then be (XIV) with the side chain β-oriented. This ester was identical with one of the two isomers which were obtained by hydrogenation of the dehydration product (IV) from methyl labdanolate, and which must have had the same configuration at $C_{(9)}$ as labdanolic acid. However the results of Dietrich, Lederer, and Mercier [6] on the reaction of osmium tetroxide in pyridine with the acid (XIII) referred to above made the above assumption questionable.

If labdanolic acid had a β-side chain at $C_{(9)}$ then one of the two hydrogenation products mentioned in the previous paragraph had to be identical with methyl dihydrocativate. This had been shown by Grant and Zeiss [8] to have structure (XVIII) while our work on labdanolic acid was in progress. The β-configuration of the side chain at $C_{(9)}$ in the ester (XVIII) followed from the conversion of cativic acid and manoöl into a common degradation product, it being assumed, of course, that the side chain of manoöl is correctly represented as β-oriented. The configuration of the 8-methyl group of the ester (XVIII) was not elucidated. Methyl dihydrocativate was, in fact, identical (mixed m. p. and identical infrared spectra) with the hydrogenation product (XIV), m. p. 44—45°, $[\alpha]_D$ +28°, which had been obtained from both the unsaturated esters (IV) and (XII) derived from

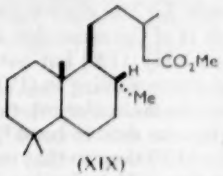
[6] Dietrich, Lederer, and Mercier, *Helv. Chim. Acta*, 1954, **37**, 705.
[7] Burn and Rigby, *Chem. and Ind.*, 1955, 386.
[8] Grant and Zeiss, *J. Amer. Chem. Soc.*, 1954, **76**, 5001.

methyl labdanolate. Labdanolic acid therefore had a side chain at $C_{(9)}$ with the same configuration (β) as that of manoöl, and hydrogenation of the ester (XII) had occurred at the α-face. The 8-methyl group in methyl dihydrocativate also had to have β-configuration (cf. XIV), while the second, liquid, hydrogenation product from (IV) could now be formulated as (XIX). We thank Dr. Harold H. Zeiss for kindly supplying us with a sample of methyl dihydrocativate. The only remaining stereochemical feature of labdanolic acid which has still to be elucidated is the configuration at position 13.

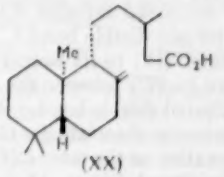
In the course of the degradation of the side chain of methyl dihydrocativate (XIV) derived from labdanolic acid we obtained the semicarbazone of the methyl ketone (XVI).



(XVIII)



(XIX)



(XX)

The melting point of our sample agreed with that quoted by Grant and Zeiss for the same compound but the rotation was only approximately half that reported. We have discussed this matter with Dr. H. Zeiss but so far have not been able to account for the difference.

When labdanolic acid had finally been shown to have structure (I) a comparison was made of the constants of its degradation products with those of the corresponding products of eperuic acid for which King and Jones [5] had proposed identical structures (excluding stereochemical differences). The comparison (cf. Table) showed that the corresponding

Structure (excluding stereochemical features) corresponding to	Constants of compound from eperuic acid		Constants of compound from labdanolic acid	
	$[\alpha]_D$ *		$[\alpha]_D$ *	
(IV)	−28·2°	n_D^{18} 1·4982	+27°	n_D^{18} 1·4980
				n_D^{20} 1·4969
(XIV)	−26·3	n_D^{18} 1·4902	+28	n_D^{20} 1·4902 (M. p. 44—45°)
Oxime of the acid corresponding to (V)	−79·4 (in dioxan)	M. p. 223°	+74·5 (in dioxan)	M. p. 188—190°
(XXV)	—	n_D^{18} 1·5520	+116	n_D^{20} 1·5520
(XV)	—	n_D^{17} 1·5010	+49	M. p. 92—93·5°
(XXVI)	−24·4	M. p. 116°	+36	M. p. 118—120°
(XVII)	−29·9	M. p. 134—135°	+40·5	M. p. 141—143° †

* In $CHCl_3$. † Undepressed on admixture with an authentic sample supplied by Dr. Rigby.

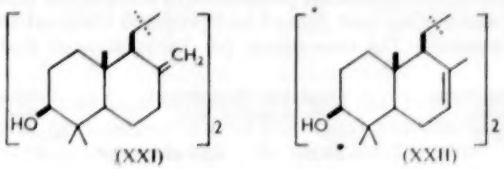
compounds had identical or similar constants except that the *sign* of the rotation was always opposite. This suggests the startling conclusion that eperuic acid is (XX) and has a carbon skeleton which is the mirror image of that of rings A and B of all the hitherto known natural di- and tri-terpenes and steroids.

[*Note added September 13th*, 1956.—Dr. F. E. King and Dr. G. Jones kindly provided us with a small sample of methyl eperuate freshly prepared from eperuic acid obtained from wallaba exudate. As noted by them, its rotation proved to be lower ($[\alpha]_D$ −47°) than that previously reported ($[\alpha]_D$ −28°).[5] Its infrared spectrum was identical with that of the dehydration product (IV) of methyl labdanolate except that the bands at 890 and 1645 cm.$^{-1}$ were less intense. This indicated that the methyl eperuate sample contained an isomer having a double bond and the most likely one appeared to be that corresponding to structure (XII). In the labdanolic acid series this has a rotation of $[\alpha]_D$ +64° and its mirror image would hence have $[\alpha]_D$ −64°, *i.e.*, more negative than that of methyl eperuate. Further, this isomer might well arise during the methylation of eperuic acid with methanolic sulphuric acid (0·6%) [5] as use of 6% methanolic sulphuric acid brings about isomerisation of the *exo*methylene ester (IV) to the ester (XII). To test these views a small amount of

the methyl eperuate was refluxed for 6 hr. with methanolic sulphuric acid. The resulting product had $[\alpha]_D$ −63° and its infrared spectrum (liquid film) was identical with that of the ester (XII). These results support the conclusion suggested above.]

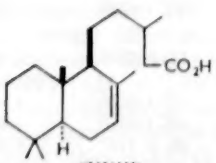
The double bond of the ester (IV) is very similarly situated to those of α-onocerin (XXI).[9] The acidic isomerisation of the exocyclic double bond of the ester (IV) to the tetrasubstituted position in the isomer (X) was in apparent contrast to the shift to the trisubstituted position which was proposed by Barton and Overton[9] to explain the acidic isomerisation of α-onocerin to β-onocerin (proposed structure XXII). Barton and Overton[9] themselves commented that the proposed course of the isomerisation was unexpected.

The molecular-rotation difference for the conversion of α-onocerin into β-onocerin is +205° for one double bond.[9] This is of the same sign as that found for the isomerisation of the ester (IV) to its isomer [(+)-XII] (119°) but not as that of the molecular-rotation difference (−97°) between the acid corresponding to (IV) and cativic acid (XXIII)[8] with a trisubstituted double bond. Again the molecular-rotation difference found on hydrogenating β-onocerin diacetate (−154° for one double bond[9]) is much closer to that found on hydrogenation of the ester (XII) (−112°) than to that occurring when cativic acid (XXIII) is hydrogenated (+ *ca.* 113°; in this calculation the rotation of dihydrocativic acid is assumed to be the same as that of methyl dihydrocativate). These results suggest that β-onocerin has in fact structure (XXIV), and Professor D. H. R. Barton and Dr. K. H. Overton have kindly informed us that they now have evidence (unpublished) which supports the new tetrasubstituted positions for the double bonds in β-onocerin.

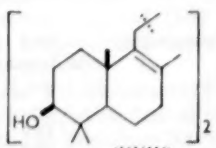


(XXI)

(XXII)



(XXIII)



(XXIV)

Experimental

Rotations refer to solutions in $CHCl_3$ (unless otherwise stated) at room temperature. M. p.s were determined on a Kofler block and are corrected. The alumina used for chromatography had an activity I—II unless otherwise stated. Light petroleum refers to the fraction with b. p. 60—80°. Unless stated otherwise ultraviolet spectra were determined on ethanol and infrared data on carbon disulphide solutions.

Methyl Labdanolate Acetate (*Methyl 8α-Acetoxylabdan-15-oate*).—Methyl labdanolate (960 mg.) in chloroform (15 c.c.) was heated under reflux for 17 hr. with dimethylaniline (18 c.c.) and acetyl chloride (4 c.c.). After the resultant deep blue solution had been diluted with water and acidified with dilute hydrochloric acid, ether-extraction afforded a product which was adsorbed from pentane on alumina (60 g.; activity II). Elution with pentane–benzene (9 : 1) yielded a liquid fraction (170 mg.) which was identified as methyl labd-8(20)-en-15-oate, $[\alpha]_D$ +27° (*c*, 1·03), n_D^{18} 1·4980, identical infrared spectrum (see below). Elution with benzene gave *methyl 8α-acetoxylabdan-15-oate* as needles (300 mg.) (from slightly aqueous methanol), m. p. 84—84·5°, $[\alpha]_D$ −29° (*c*, 1·15) (Found: C, 72·6; H, 10·35. $C_{23}H_{40}O_4$ requires C, 72·6; H, 10·6%).

Attempted Oxidation of Methyl Labdanolate.—Methyl labdanolate (100 mg.) in acetone

[9] Barton and Overton, *J.*, 1955, 2639.

(15 c.c.) was treated with chromic acid (8N) according to the method of Bowers *et al.*[10] After dilution with water, ether-extraction afforded unchanged starting material as needles (from pentane), m. p. and mixed m. p. 73—74°.

Reduction of Methyl Labdanolate.—Methyl labdanolate (580 mg.) in ether (15 c.c.) was slowly added to a slurry of lithium aluminium hydride (300 mg.) in ether (15 c.c.). The mixture was heated under reflux for 1 hr. and then kept at 20° overnight. After decomposition of an excess of the reagent with ethyl acetate and acidification ether-extraction afforded a solid which was recrystallised from pentane, to give *labdane*-8α : 15-*diol* (III) as cubes, m. p. 84—85°, $[\alpha]_D$ −7° (*c*, 1·7) (Found: C, 77·25; H, 12·3. $C_{20}H_{34}O_2$ requires C, 77·35; H, 12·35%). Acetylation with pyridine–acetic anhydride at 20° for 18 hr. gave *labdane*-8α : 15-*diol* 15-*monoacetate* which, after purification by chromatography on alumina deactivated with 5% of 10% aqueous acetic acid, was obtained as a gum, $[\alpha]_D$ −3·7° (*c*, 0·98), n_D^{19} 1·4944 (Found: C, 74·85; H, 11·25. $C_{22}H_{40}O_3$ requires C, 74·95; H, 11·45%). Infrared absorption bands at 1238, 1746, and 3615 cm.$^{-1}$.

Dehydration of Methyl Labdanolate.—Methyl labdanolate (26·8 g.) in pyridine (360 c.c.) was treated with phosphoryl chloride (70 c.c.). After 15 hr. at 20° it was added dropwise, with stirring, to ice and water (3 l.). Ether-extraction afforded a product which was adsorbed from light petroleum on alumina (120 g.). Elution with light petroleum–benzene (4 : 1; 400 c.c.) gave *methyl labd*-8(20)-*en*-15-*oate* (IV) (24·3 g., 96%) as a syrup, $[\alpha]_D$ +27° (*c*, 2·31), n_D^{18} 1·4980, n_D^{20} 1·4969 (Found: C, 78·85; H, 11·3. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·3%). Infrared absorption bands at 890, 1645, and 1745 cm.$^{-1}$. Hydrolysis of the ester with ethanolic sodium hydroxide gave *labd*-8(20)-*en*-15-*oic acid* as a gum, $[\alpha]_D$ +25° (*c*, 0·97) (Found: C, 78·35; H, 11·1. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%). The cyclo*hexylamine salt*, prepared as described above, was crystallised to constant rotation from ethyl acetate as needles, m. p. 123—136° (dependent upon rate of heating), $[\alpha]_D$ +22° (*c*, 0·78) (Found: C, 77·35; H, 11·8; N, 3·35. $C_{26}H_{47}O_2N$ requires C, 77·0; H, 11·7; N, 3·45%).

Ozonolysis of Methyl Labd-8(20)-*en*-15-*oate* (IV).—The ester (0·92 g.) in ethyl acetate (200 c.c.) was treated with ozonised oxygen at −70° until a faint blue colour persisted in the solution. The excess of ozone was removed by passing a stream of nitrogen through the solution for 10 min. The mixture was then stirred with acetic acid (18 c.c.) and zinc dust (4 g.) until it no longer gave a colour with a starch–iodide paper (approx. 45 min.). The zinc was removed and the filtrate washed with water. The aqueous washings, on treatment with a methanolic solution of 2 : 4-dinitrophenylhydrazine sulphate, gave formaldehyde 2 : 4-dinitrophenylhydrazone (40 mg., 30%), m. p. and mixed m. p. 166—167°. Evaporation of the organic phase gave methyl 20-nor-8-oxo-labdan-15-oate (V) as a gum, with infrared absorption bands at 1709 and 1736 cm.$^{-1}$. The ester was characterised by hydrolysis with methanolic 2N-potassium hydroxide under reflux for 1 hr., 20-*nor*-8-*oxolabdan*-15-*oic acid* being obtained as prismatic needles (from methanol–water), m. p. 110·5—111°, $[\alpha]_D^{14}$ −40° (*c*, 1·01) (Found: C, 74·1; H, 10·55. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·45%). Light absorption max. (in EtOH) at 2880 Å (ε 31). Infrared absorption band at 1703 cm.$^{-1}$. The keto-acid (76 mg.) in ethanol (0·5 c.c.) and hydroxylamine hydrochloride (0·163 g.) in water (1 c.c.) were treated with 2N-sodium hydroxide until just alkaline, then heated under reflux on the steam-bath for 30 min. After cooling, acidification with hydrochloric acid gave a precipitate, m. p. 184—188°, which crystallised from aqueous ethanol to give the *oxime* (62 mg.) as prisms, m. p. 188—190° after softening at 170°, $[\alpha]_D$ +74·5° (*c*, 1·14 in dioxan) (Found: C, 70·7; H, 10·25. $C_{19}H_{33}O_3N$ requires C, 70·55; H, 10·3%).

Reduction of Methyl Labd-8(20)-*en*-15-*oate* (IV).—The ester (2·0 g.) in ether (40 c.c.) was treated with a 0·76% solution of lithium aluminium hydride in ether (45 c.c.). After 1 hr. at 0°, water and then dilute acetic acid were added. Ether-extraction gave labd-8(20)-en-15-ol (VI) as a gum (1·75 g.), $[\alpha]_D$ +40° (*c*, 0·98). Infrared absorption bands at 890, 1645, 3090, and 3645 cm.$^{-1}$. The gum was not analysed but converted directly into the triol by reaction with osmium tetroxide.

Labd-8(20)-en-15-ol (1·60 g.) in pyridine–chloroform (1 : 1; 100 c.c.) was treated with osmium tetroxide (2 g.) and kept at 20° for 6 days. Removal of the solvents under reduced pressure gave a black residue which was heated under reflux for 3 hr. with benzene (35 c.c.), methanol (35 c.c.), potassium hydroxide (8 g.), and mannitol (8 g.) in ethanol (35 c.c.) and water (22 c.c.). After dilution with water, ether-extraction gave a gum (1·68 g.) which was adsorbed from benzene on alumina (100 g.) deactivated with 7·5% of 10% acetic acid. Elution with

[10] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

ether gave *labdane*-8α : 15 : 20-*triol* (VII) as needles (0·343 g.) (twice crystallised from light petroleum–benzene), m. p. 124—125·5°, $[\alpha]_D$ −17° (*c*, 1·01) (Found: C, 73·45; H, 11·7. $C_{20}H_{38}O_3$ requires C, 73·55; H, 11·75%). Infrared absorption in carbon tetrachloride: broad band at 3400 cm.$^{-1}$.

Dehydrogenation of 15-*Hydroxylabd*-8(20)-*ene* (VI).—A mixture of 15-hydroxylabd-8(20)-ene (1·83 g.) and platinum-on-carbon (30%; 0·44 g.; prepared according to Vogel [11]) was heated at 315—330° for 48 hr. After cooling, the product was isolated by continuous ether-extraction. Removal of the ether gave a yellow oil (1·32 g.) which was adsorbed from light petroleum on alumina (200 g.). Elution with light petroleum gave two main oily fractions [(i) 650 and (ii) 144 mg.]. Elution with light petroleum–benzene (10 : 1) gave one main fraction [(iii) 54 mg.]. Further elution with light petroleum–benzene (4 : 1) and with benzene eluted only small amounts of material.

Fraction (i) consisted of non-aromatic hydrocarbons, b. p. 176° (bath-temp.)/10 mm., n_D^{17} 1·4868 (Found: C, 86·4; H, 13·1. Calc. for $C_{20}H_{36}$: C, 86·9; H, 13·1. Calc. for $C_{20}H_{38}$: C, 86·25; H, 13·75%). The infrared spectrum had no bands corresponding to an aromatic ring system; there were bands at 1368, 1388, and 1466 cm.$^{-1}$.

Fraction (ii) was 1 : 2 : 5-trimethylnaphthalene. Light absorption max. in hexane were at 2260, 2310, 2780, 2890, 3000 (infl.), 3100, and 3250 Å (log ε 4·8, 4·98, 3·78, 3·80, 3·65, 3·16, and 2·94). Heilbronner, Fröhlicher, and Plattner [2] give max. at 2260 (infl.), 2300, 2780, 2880, 3000 (infl.), and 3240 Å (log ε 4·73, 4·96, 3·78, 3·87, 3·68, and 2·96). Treatment of the trimethylnaphthalene with a saturated solution of 1 : 3 : 5-trinitrobenzene in alcohol gave the adduct as yellow needles, m. p. 150—158°, raised by several recrystallisations from alcohol to 153—158° (decomp.) (slow change of crystal shape from 120°). Ruzicka, Baumgartner, and Prelog [12] give m. p. 158—159° (sealed tube) (Found: C, 60·1; H, 4·45. Calc. for $C_{19}H_{17}O_6N_3$: C, 59·55; H, 4·45; N, 10·95%).

Fraction (iii) was 1 : 2 : 5 : 6-tetramethylnaphthalene. It was converted into the 1 : 3 : 5-trinitrobenzene adduct which was obtained as orange needles (from ethanol), m. p. 179—181°. Grant and Zeiss [8] give m. p. 180—181°. The pure adduct (27·4 mg.) was adsorbed from light petroleum–benzene on alumina (2 g.). Elution with the same solvent (8 c.c.) gave 1 : 2 : 5 : 6-tetramethylnaphthalene (12·5 mg.), m. p. 112·5—115°. Grant and Zeiss [8] give 114·5—115°. On the assumption that the two components of the adduct have a 1 : 1 molar ratio the weight of hydrocarbon recovered indicates a mol. wt. of 189 (Calc. for tetramethylnaphthalene: *M*, 184).

Isomerisation of Methyl Labd-8(20)-*en*-15-*oate* (IV).—Methyl labd-8(20)-en-15-oate (24·2 g.) in benzene (400 c.c.) was heated under reflux with methanolic sulphuric acid (6·7%; 1200 c.c.) for 3 hr. The mixture was then evaporated under reduced pressure below 30° to half its original volume. After dilution with water, extraction with benzene afforded *methyl labd*-8-*en*-15-*oate* (XII) as an oil (23·8 g.), $[\alpha]_D$ +64° (*c*, 1·07), n_D^{24} 1·4962 (Found: C, 78·5; H, 11·3. $C_{21}H_{38}O_2$ requires C, 78·7; H, 11·3%). Light absorption in EtOH: ε_{2100} 5340; ε_{2150} 3020; ε_{2300} 1650; ε_{2250} 850. Infrared absorption: no bands corresponding to a trisubstituted double bond or a vinylidene group; band at 1745 cm.$^{-1}$.

The ester (5 g.) was hydrolysed under reflux for 1 hr. with a solution from sodium (3·5 g.) in ethanol (100 c.c.) and water (2 c.c.). The resulting acidic fraction was crystallised several times from slightly aqueous methanol, to give *labd*-8-*en*-15-*oic acid* as needles, m. p. 110·5—112°, $[\alpha]_D$ +69° (*c*, 1·06) (Found: C, 78·15; H, 11·35. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%).

Action of Osmium Tetroxide on Labd-8-*en*-15-*oic Acid.*—Labd-8-en-15-oic acid (0·20 g.) in ether (15 c.c.) was treated with osmium tetroxide (0·217 g.; 20% excess) in ether (15 c.c.) and pyridine (0·3 c.c.) for 6 days at 20°. Removal of the solvents under reduced pressure gave a solid which was shaken for 15 min. with potassium hydroxide (2·8 g.) and mannitol (2·8 g.) in water (50 c.c.) and dioxan (30 c.c.). After dilution with water and acidification with 2N-hydrochloric acid, ether-extraction afforded crystals (0·18 g.), m. p. 122—126°, which, recrystallised several times from light petroleum, gave 8ξ : 9ξ-*dihydroxylabdan*-15-*oic acid* as cubes (0·185 g.), m. p. 125—126°, $[\alpha]_D$ −1·8° (*c*, 1·06) (Found: C, 70·85; H, 10·95. $C_{20}H_{36}O_4$ requires C, 70·55; H, 10·65%).

Hydrogenation of Methyl Labd-8(20)-*en*-15-*oate* (IV).—Methyl labd-8(20)-en-15-oate (10·32 g.) in acetic acid (90 c.c.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (0·51 g.). The uptake of hydrogen ceased after 15 min. After removal of the catalyst, evaporation under reduced pressure gave an oily solid, $[\alpha]_D$ +15° (*c*, 1·54). The oil was

[11] Vogel, "A Text Book of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 823.

[12] Ruzicka, Baumgartner, and Prelog, *Helv. Chim. Acta*, 1949, **32**, 2057.

removed by pressing the oily solid on porous tiles. The residual solid, m. p. 36—42°, $[\alpha]_D$ +23°, was recrystallised several times from methanol to give methyl labdan-15-oate (methyl dihydrocativate) (XIV) as flat spars (5 g.), m. p. 44—45°, undepressed on admixture with a sample of methyl dihydrocativate, m. p. 44—45°, kindly supplied by Dr. Harold H. Zeiss,[9] $[\alpha]_D$ +28° (*c*, 1·0), n_D^{20} 1·4902 (Found: C, 78·25; H, 11·85. Calc. for $C_{21}H_{38}O_2$: C, 78·2; H, 11·9%). Continuous extraction of the oil from the porous tiles with ether gave impure methyl 8β(H)-labdan-15-oate (XIX) as an oil (3·0 g.), $[\alpha]_D$ +14° (*c*, 1·09), n_D^{20} 1·4900. Hydrolysis of the ester with ethanolic sodium hydroxide gave 8β(H)-labdan-15-oic acid as a gum which was characterised as its cyclo*hexylamine salt*. This was crystallised from ethyl acetate to constant rotation to give needles, $[\alpha]_D$ +14° (*c*, 1·07) (Found: C, 76·9; H, 12·05; N, 3·25. $C_{26}H_{49}O_2N$ requires C, 76·6; H, 12·1; N, 3·45%).

Hydrogenation of Methyl Labd-8-en-15-oate (XII).—Methyl labd-8-en-15-oate (23·4 g.) in acetic acid (150 c.c.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (1 g.). The uptake of hydrogen ceased after 1 hr. After removal of the catalyst, evaporation under reduced pressure gave a solid, m. p. 40—42°, $[\alpha]_D$ +23·5° (*c*, 0·96). This was crystallised twice from methanol to give methyl labdan-15-oate (XIV) as flat spars, m. p. 44—45°, undepressed on admixture with a sample prepared by hydrogenation of methyl labd-8(20)-en-15-oate.

Hydrogenation of Labd-8-en-15-oic Acid.—Labd-8-en-15-oic acid (60 mg.) in acetic acid (20 c.c.) was hydrogenated at atmospheric pressure in the presence of pre-reduced Adams catalyst (100 mg.). After the uptake of hydrogen had ceased, filtration and evaporation gave the product as a gum. This was methylated with ethereal diazomethane, to give methyl labdan-15-oate as flat spars (from methanol), m. p. and mixed m. p. 44—44·5°.

Treatment of Methyl Labdan-15-oate (XIV) *with Phenylmagnesium Bromide*.—Methyl labdan-15-oate (4·4 g.) in ether (50 c.c.) was slowly added to the Grignard reagent from magnesium (2·8 g.) and bromobenzene (15 g.) in ether (120 c.c.). The mixture was then heated under reflux for 1½ hr. and kept overnight at 20°. After addition of ammonium chloride solution, ether-extraction gave a product which was adsorbed from light petroleum on alumina (250 g.). After elution with light petroleum to remove bromobenzene and diphenyl, elution with ether (1200 c.c.) gave a fraction (87% yield), m. p. 77—82°, which, crystallised from aqueous methanol, gave 15 : 15-*diphenyl-labdan-15-ol* as plates, m. p. 85—86°, $[\alpha]_D$ +10·5° (*c*, 0·94) (Found: C, 85·8; H, 10·65. $C_{32}H_{44}O$ requires C, 86·05; H, 10·4%).

The alcohol (5·3 g.) in acetic acid (60 c.c.) and acetic anhydride (10 c.c.) was heated under reflux for 2¼ hr. After removal of the solvents under reduced pressure the viscous product was adsorbed from light petroleum on alumina (200 g.). Elution with light petroleum (1600 c.c.) afforded 15 : 15-*diphenyl-labd-14-ene* (XXV) (4·8 g., 82%) as an oil, $[\alpha]_D$ +116° (*c*, 0·81), n_D^{20} 1·5520 (Found: C, 89·15; H, 10·7. $C_{32}H_{44}$ requires C, 89·65; H, 10·35%). Light absorption max. in *cyclo*hexane at 2515 Å (ε 14,100). In later preparations the crude alcohol was crystallised once and then dehydrated.

Oxidation of 15 : 15-*Diphenyl-labd-14-ene* (XXV).—(i) Chromic acid (0·64 g.) in acetic acid (7 c.c.) and water (2 c.c.) was added during 1 hr. to a stirred solution of 15 : 15-diphenyl-labd-14-ene (0·905 g.) in acetic acid (10 c.c.) and chloroform (8 c.c.) at 22°. Stirring was continued for a further hour and then the solvents were removed at 30° under reduced pressure. The residue was divided into acidic and neutral fractions (0·16 g. and 0·705 g.). The neutral fraction in acetic acid (10 c.c.) and chloroform (8 c.c.) was re-oxidised with chromic acid (0·40 g.) in acetic acid (7 c.c.) and water (1 c.c.) for 3 hr. at 60° and then overnight at 20°. Methanol (2 c.c.) was then added and the acidic product isolated. Several crystallisations of the total acidic material (0·295 g.) from aqueous methanol gave 15-*norlabdan-14-oic acid* (XV) as needles, m. p. 92—93·5°, $[\alpha]_D$ +49° (*c*, 1·0) (Found: C, 77·5; H, 11·5. $C_{19}H_{34}O_2$ requires C, 77·5; H, 11·65%).

(ii) 15 : 15-Diphenyl-labd-14-ene (6·91 g.) in chloroform (120 c.c.) was treated with a stream of ozonised oxygen at −50°, until the solution turned faintly blue. The excess of ozone was removed by passing a stream of nitrogen through the solution for 10 min., and then the ozonide was decomposed by zinc dust (8 g.) and acetic acid (40 c.c.). The mixture was allowed to warm to 20° and then stirred until it no longer gave a colour with starch–iodide paper. Filtration and evaporation under reduced pressure at 60° gave an oil which was oxidised in acetic acid (100 c.c.) with chromic acid (1·7 g.) in water (4 c.c.) for 20 hr. at 20°. The solvents were then removed under reduced pressure and the acidic product isolated, to give 15-norlabdan-14-oic acid (2·74 g.) as needles (from aqueous methanol), m. p. 92—93°.

Methylation of the acid (4·09 g.) with an excess of ethereal diazomethane gave a product which was adsorbed from light petroleum on neutral alumina (150 g.). Elution with light

petroleum–benzene (7 : 1; 1600 c.c.) gave a fraction (3·635 g.) which was crystallised from methanol to give *methyl* 15-*norlabdan*-14-*oate* as needles, m. p. 58·5—59·5°, $[\alpha]_D$ +50° (*c*, 1·08) (Found: C, 77·8; H, 11·75. $C_{20}H_{36}O_2$ requires C, 77·85; H, 11·75%).

Treatment of Methyl 15-*Norlabdan*-14-*oate with Phenylmagnesium Bromide.*—Methyl 15-norlabdan-14-oate (3·63 g.) in ether (100 c.c.) was added to the Grignard reagent from magnesium (2·4 g.), bromobenzene (16 g.), and ether (140 c.c.). The mixture was then heated under reflux for 1½ hr. and kept overnight at 20°. After addition of ammonium chloride solution, ether-extraction gave an oil which was adsorbed from light petroleum on neutral alumina (200 g.). After elution with light petroleum (1200 c.c.) to remove bromobenzene and diphenyl, elution with ether (900 c.c.) gave the crude alcohol which was heated under reflux in acetic acid (100 c.c.) and acetic anhydride (30 c.c.). After removal of the solvents under reduced pressure the product was adsorbed from light petroleum on alumina (200 g.). Elution with light petroleum (900 c.c.) afforded a fraction, m. p. 110—115°, which was crystallised from methanol–chloroform to give 14 : 14-*diphenyl*-15-*norlabd*-13-*ene* (XXVI) as plates (3·0 g.), m. p. 118—120°, $[\alpha]_D$ +36° (*c*, 1·07) (Found: C, 89·9; H, 10·2. $C_{31}H_{42}$ requires C, 89·8; H, 10·2%). Light absorption max. in *cyclo*hexane at 2450 Å (ε 13,800).

Ozonisation of 14 : 14-*Diphenyl*-15-*norlabd*-13-*ene* (XXVI).—The hydrocarbon (0·43 g.) in ethyl acetate (40 c.c.) was treated with a slow stream of ozonised oxygen at −60° until the solution became faintly blue. After the excess of ozone had been removed in nitrogen, acetic acid (10 c.c.) and zinc dust (3 g.) were added. The mixture was allowed to warm to 20° and was then stirred until it no longer gave a colour with a starch–iodide paper. Filtration and evaporation under reduced pressure gave a product which was taken up in ether, washed with potassium hydrogen carbonate solution, and dried. Evaporation gave an oily mixture (0·448 g.) of benzophenone and 15 : 16-bisnorlabdan-13-one (XVI), having infrared absorption bands at 1663 and 1712 cm.$^{-1}$.

The latter ketone was separated from the benzophenone as follows: (a) *Preferential formation of the* 2 : 4-*dinitrophenylhydrazone.* The mixture of ketones (208 mg.) in methanol (3 c.c.) was treated with methanolic 2 : 4-dinitrophenylhydrazine sulphate (2½%; 8 c.c.). After 5 min. at 20° the yellow precipitate which had formed was separated, dissolved in benzene (100 c.c.), and filtered through neutral alumina (15 g.), to give 15 : 16-*bisnorlabdan*-13-*one* 2 : 4-*dinitrophenylhydrazone* (126 mg.) as flat spars (from 95% ethanol), m. p. 148—149° with change in crystalline form to needles at 144° (Found: C, 65·0; H, 8·4; N, 12·7. $C_{24}H_{36}O_4N_4$ requires C, 64·85; H, 8·15; N, 12·6%).

(b) *Preferential formation of the semicarbazone.* The mixture of ketones (1 g.) in ethanol (2 c.c.) was treated with the filtrate from a mixture of semicarbazide hydrochloride (1 g.), sodium acetate (1·5 g.), water (2 c.c.), and ethanol (7 c.c.). After 10 min. at 20° the precipitated semicarbazone was separated. Repeated recrystallisation from ethanol gave 15 : 16-bisnorlabdan-13-one semicarbazone as needles, m. p. 199—201° with softening at 194°, $[\alpha]_D$ +36·5° (*c*, 1·0) (Found: C, 71·05; H, 11·0; N, 12·5. Calc. for $C_{19}H_{35}ON_3$: C, 71·0; H, 10·95; N, 13·05%). Grant and Zeiss [8] give m. p. 201·5—202°, $[\alpha]_D$ +66·6°.

Hydrolysis of 15 : 16-*Bisnorlabdan*-13-*one* 2 : 4-*Dinitrophenylhydrazone.*—The dinitrophenylhydrazone (95 mg.) in acetone (20 c.c.) was heated under reflux for 45 min. with hydrochloric acid (0·5 c.c.). Stannous chloride (500 mg.) in hydrochloric acid (2 c.c.) was added and the mixture heated under reflux for a further 45 min. under nitrogen. After removal of acetone at 20° under reduced pressure, the residue was extracted with benzene. The extract was washed with N-hydrochloric acid until no more coloured material was removed, and then evaporated to give 15 : 16-bisnorlabdan-13-one as an oil (50 mg.), having infrared absorption bands at 1711, 1408, and 1355 cm.$^{-1}$, due to a carbonyl group, a methylene group adjacent to a keto-group, and to a methyl group adjacent to a keto-group respectively.

Hydrolysis of 15 : 16-*Bisnorlabdan*-13-*one Semicarbazone.*—The semicarbazone (0·21 g.) was hydrolysed according to the method of Braude *et al.*[13] under reflux in light petroleum (40 c.c.) with 5% sulphuric acid (25 c.c.) for 18 hr. The light petroleum phase was then separated, washed, dried, and evaporated to give the ketone as an oil (0·165 g., 94%). Its infrared spectrum was identical with that of the oil from the dinitrophenylhydrazone.

Oxidation of 15 : 16-*Bisnorlabdan*-13-*one* (XVI).—The ketone (0·165 g.) in dioxan (10 c.c.) was treated with a solution of potassium iodide (1·0 g.) in water (1·5 c.c.) and 2N-potassium hydroxide solution (2 c.c.). Sodium hypochlorite solution (0·9 c.c.) was then added dropwise during 10 min. at 30°. The mixture was kept at 20° for 30 min. more and then diluted with

[13] Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890.

water and extracted with ether to remove non-acidic material. The aqueous phase was treated with a small quantity of sodium hydrogen sulphite, acidified with hydrochloric acid, and extracted with ether. Extraction of the ether solution with potassium hydroxide solution, followed by acidification of the alkaline phase and further extraction with ether gave the acidic product as a gummy solid. Several recrystallisations of this from aqueous methanol gave 14 : 15 : 16-trisnorlabdan-13-oic acid as needles (30 mg.), m. p. 141—143° (change of crystal form at 125°), undepressed on admixture with an authentic sample kindly supplied by Dr. W. Rigby, $[\alpha]_D$ +40·5° (*c*, 1·02) (Found : C, 76·7; H, 11·1. Calc. for $C_{17}H_{30}O_2$: C, 76·65; H, 11·35%). The infrared spectrum (" Nujol " paste) was identical with that of an authentic sample.

[*Added September 13th, 1956.*—*Isomerisation of methyl eperuate.* Methyl eperuate (200 mg.) {$[\alpha]_D$ −47° (*c*, 1·24)}, freshly prepared by Dr. F. E. King and Dr. G. Jones from eperuic acid obtained from wallaba exudate, was refluxed with methanolic sulphuric acid (6·7%; 90 c.c.) for 6 hr. and then kept overnight. After dilution with water, the product was extracted with benzene. The extract was washed with water and dried (Na_2SO_4). Evaporation of the benzene gave a liquid, $[\alpha]_D$ −63·5° (*c*, 1·21). The infrared spectrum (liquid film) of the liquid was identical in every respect with that (liquid film) of methyl labd-8-en-15-oate (XII), $[\alpha]_D$ +64° (*c*, 1·07).]

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821. *The Formation of Nitrosochlorides and Nitrosates.*

By N. Thorne.

In an investigation of the effect of structure on the ease of formation of nitrosochlorides and nitrosates by olefinic compounds it has been shown that, in general, structures which increase the availability of electrons at the double bond favour these addition reactions. Terminal double-bond compounds have been investigated in some detail.

The addition of nitrosyl chloride to compounds containing carbon-to-carbon double bonds has been studied extensively, especially in the terpene series. Many double-bond compounds other than terpenes form nitrosochlorides, but some do not. Tilden and Sudborough [1] found that while trimethylethylene and styrene with nitrosyl chloride form crystalline dimeric nitrosochlorides, ethylene forms a dichloride, and propene and but-2-ene yield mixtures of dichloride and nitrosochloride. Tilden and Forster [2] showed that hex-2-ene and octene yield nitrosochlorides which were isolated in the form of monomeric blue oils, that stilbene and oleic acid form nitrosochlorides, but that β-nitrostyrene, phenanthrene, acenaphthylene, crotonic acid, but-3-enoic acid, maleic acid, fumaric acid, cinnamic acid, and ethyl cinnamate do not. They concluded that the proximity of a nitro- or carboxyl group to the ethylene carbon atoms seems to prevent the addition of nitrosyl chloride. A review on nitrosyl chloride [3] shows that nitrosochlorides of compounds such as ethylene have recently been prepared by utilising catalysts, and in some cases by working at very low temperatures.

In the work now described, the usual conditions for the preparation of nitrosochlorides and nitrosates were adopted, namely, mixing the olefin and pentyl nitrite, in a solvent if necessary, cooling in salt–ice, and adding fuming hydrochloric acid dropwise with stirring.

[1] Tilden and Sudborough, *J.*, 1893, **63**, 479.
[2] Tilden and Forster, *J.*, 1894, **65**, 324.
[3] Beckham, Fessler, and Kise, *Chem. Rev.*, 1951, **48**, 369.

In the preparation of nitrosates, the cooled mixture of the olefin and pentyl nitrite was allowed to react with concentrated nitric acid.

The extent to which the carboxyl group inhibits formation of nitrosochlorides was investigated for 4-phenylbut-3-enoic and 5-phenylpent-4-enoic acid. Neither of these forms a nitrosochloride or nitrosate, despite the fact that in the pentenoic acid the double bond and the carboxyl group are separated by two methylene groups. Oleic acid forms a nitrosochloride,[2] but in this case seven methylene groups intervene. It is therefore evident that a carboxyl group has a very marked effect, and that nitrosochloride formation does not take place unless the carboxyl group is well removed from the double bond.

Among hydrocarbons the position of the double bond in the carbon chain is found to affect the reaction. Allylbenzene does not form a nitrosochloride while propenylbenzene does. Hex-1-ene, hept-1-ene, and oct-1-ene do not form adducts, but hex-2-ene, hept-2-ene, oct-2-ene, and 4-methylpent-2-ene give low yields of monomeric nitrosochlorides. Nitrosate formation follows the same pattern, except that in the case of hex-2-ene a fair yield of the dimeric nitrosate is obtained. These results show that nitrosochlorides and nitrosates are not formed when the unsaturation is in the form of the allyl group $CH_2{:}CH{\cdot}CH_2{\cdot}$, although the propenyl structure $CH_3{\cdot}CH{:}CH$ permits their formation. This is supported by the researches of Tilden and Forster,[2] who showed that eugenol and safrol (allylic unsaturation) do not form nitrosochlorides, while anethole and *iso*safrole (propenylic unsaturation) do. It is found that hydrocarbons which possess a terminal double bond without conforming to the allylic structure usually form nitrosochlorides but not nitrosates. Thus 2 : 4 : 4-trimethylpent-1-ene readily forms a nitrosochloride but not a nitrosate; styrene forms a nitrosochloride, but allylbenzene (allylic structure) does not. The double bonds in the allyl and the propenyl structure are so similar in their other reactions that this difference is surprising.

Nitro-groups inhibit formation of the nitrosochloride since none of the nitro-substituted styrenes forms adducts.

It can be seen from the Table that methyl- and methoxy-substituted olefins usually

Compound	Yield (%) of: nitrosochloride	nitrosate
Trimethylethylene	52	50
4-Phenylbut-3-enoic acid	—	—
5-Phenylpent-4-enoic acid	—	—
Allylbenzene	—	—
Propenylbenzene	32	—
Hex-1-ene	—	—
Hex-2-ene	4—5(monomer)	20
Hept-1-ene	—	—
Hept-2-ene	4—5(monomer)	4—5(monomer)
Oct-1-ene	—	—
Oct-2-ene	4—5(monomer)	4—5(monomer)
4-Methylpent-2-ene	4—5(monomer)	4—5(monomer)
2 : 4 : 4-Trimethylpent-1-ene	40	—
2 : 4 : 4-Trimethylpent-2-ene	68	47

Compound	Yield (%) of nitrosochloride
Styrene	30 •
α-Methylstyrene	71
α : 4-Diethylstyrene	27
2-Methylstyrene	52
3-Methylstyrene	32
4-Methylstyrene	66
2 : 4 : 6-Trimethylstyrene	—
2-, 3-, and 4-Nitrostyrene	—
o-Methoxypropenylbenzene	60
m-Methoxypropenylbenzene	34
p-Methoxypropenylbenzene	79
1 : 1-Diphenylethylene	—
1 : 1-Di-*p*-methoxyphenylethylene	—

• None of the compounds in this column forms a nitrosate.

give high yields of nitrosochlorides. α-Methylstyrene gives a much higher yield than styrene, although α : 4-dimethylstyrene gives a lower yield. This may be due to the fact that α : 4-dimethylstyrene nitrosochloride is very unstable and therefore probably decomposes during its preparation. Methyl and methoxy-groups have little effect when in the *meta*-position, since 3-methylstyrene and styrene, and *m*-methoxypropenylbenzene and propenylbenzene give approximately the same yields of adducts.

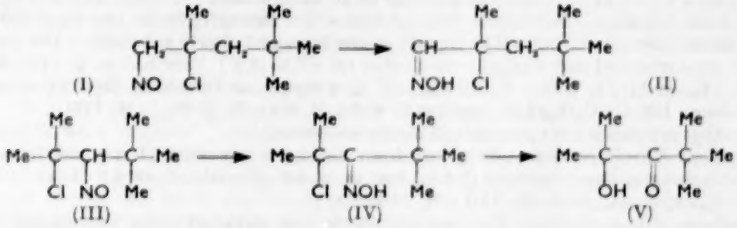
2 : 4 : 6-Trimethylstyrene does not form a nitrosochloride, probably owing to the steric effect of the two *o*-methyl groups. Similarly the steric effect of the phenyl groups in 1 : 1-diphenylethylene and 1 : 1-di-*p*-methoxyphenylethylene probably prevents these compounds from forming adducts.

In the case of the aliphatic olefins, low yields of adducts are isolated from hex-2-ene, hept-2-ene, oct-2-ene, and 4-methylpent-2-ene, but yields are better from trimethylethylene

and 2 : 4 : 4-trimethylpent-1- and -2-ene. In the last compounds, the methyl groups increase the overall availability of electrons at the double bond. The same is true of the methyl and methoxy-substituted aryl olefins, especially when *ortho* or *para*. Nitro- and carboxyl groups have the reverse effect, and tend to reduce the electron-availability. It is therefore evident that nitrosochlorides are more readily formed by olefins containing groups which will reduce the reactivity of the double bond towards nucleophilic reagents, and increase it towards electrophilic reagents. It is reasonable to conclude that nitrosochlorides are formed by the combination of the electrophilic fragment NO^+, followed by the nucleophilic Cl^-.

None of the aryl olefins formed nitrosates under the conditions employed in the reaction.

Molecular-weight determinations have been carried out on all the solid nitrosochlorides and nitrosates obtained; these products are dimeric in benzene at about 5°, but in naphthalene at 80° are practically completely monomeric.



Isomerisation of some of the nitrosochlorides to the corresponding chloro-oximes[4] has been carried out. 2 : 4 : 4-Trimethylpent-1-ene nitrosochloride (I) isomerised to 2-chloro-1-hydroxyimino-2 : 4 : 4-trimethylpentane (II), but 2 : 4 : 4-trimethylpent-2-ene nitrosochloride (III) gave 2-chloro-3-hydroxyimino-2 : 4 : 4-trimethylpentane (IV), which on hydrolysis with dilute acid yielded 2-hydroxy-2 : 4 : 4-trimethylpentan-3-one (V).

The structures of the nitrosochlorides (I) and (III) are based on their easy isomerisation to the respective oximes (II) and (IV). This type of reaction has been studied in the case of trimethylethylene nitrosochloride,[5] and the product identified beyond reasonable doubt. If 2 : 4 : 4-trimethylpent-1-ene nitrosochloride and 2 : 4 : 4-trimethylpent-2-ene nitrosochloride undergo this isomeric change, then the carbon atom carrying the nitroso-group must also carry a hydrogen atom. This condition is satisfied by the structures (I) and (III), but would not be fulfilled if the positions of the nitroso-group and the chlorine atom were interchanged. Confirmation is provided by the fact that the mechanism of the addition is such that the chlorine atom will become attached to the carbon atom carrying the least number of hydrogen atoms.

The piperidides from all the solid nitrosochlorides formed during this work have been prepared, and in the case of propenylbenzene nitrosochloride its reactions with other bases have also been studied.

Experimental

Propenylbenzene Nitrosochloride.—Fuming hydrochloric acid (40 c.c.) was added dropwise to a mixture of propenylbenzene (20 g.) and pentyl nitrite (40 c.c.) at <0°. The solution was stirred during the addition of the acid (1½ hr.). It became greenish-blue and slowly solidified. The crystals of *propenylbenzene nitrosochloride* were removed, and washed with ice-cold ethanol till white (10·5 g.), m. p. 128° [Found: C, 58·9; H, 5·5; N, 7·65; Cl, 18·9%; *M* (cryoscopic in benzene), 365; (cryoscopic in naphthalene), 207·0. $C_9H_{10}ONCl$ requires C, 58·84; H, 5·45; N, 7·6; Cl, 19·3%; *M*, 183·5]. The same conditions and quantities of reactants as in the above preparation were used in the preparation of the other nitrosochlorides.

Propenylbenzene Nitrolpiperidide.—Propenylbenzene nitrosochloride (1 g.) was heated with piperidine (1·5 g.) and alcohol (15 c.c.) for 10 min. Water was then added till the solution

[4] Thorne, *J.*, 1956, 2587.
[5] Schmidt, *Ber.*, 1902, **35**, 3729.

became faintly cloudy, and crystals of *propenylbenzene nitrolpiperidide* soon separated; recrystallised from alcohol it (1 g.) had m. p. 112° (Found: C, 72·7; H, 8·7; N, 12·2. $C_{14}H_{20}ON_2$ requires C, 72·4; H, 8·6; N, 12·1%). All the piperidides were prepared in this manner.

Propenylbenzene Nitrolanilide.—Prepared in the same way as the piperidide but with aniline (1 g.), this *compound* (1·2 g.) had m. p. 130° (Found: C, 75·3; H, 6·7; N, 11·8. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%).

Propenylbenzene Nitrolmethylanilide.—Prepared as above with methylaniline (1 g.), the *compound* (1·2 g.) had m. p. 148° (Found: C, 76·05; H, 7·1; N, 10·9. $C_{16}H_{18}ON_2$ requires C, 75·6; H, 7·1; N, 11·0%).

Propenylbenzene Nitrol-o-toluidide.—The *compound* (1 g.), obtained from *o*-toluidine (1 g.), had m. p. 124° (Found: C, 75·6; H, 7·1; N, 11·1. $C_{16}H_{18}ON_2$ requires C, 75·6; H, 7·1; N, 11·0%).

Propenylbenzene Nitrol-m-toluidide.—This *compound* (1·2 g.) had m. p. 143° (Found: C, 75·6; H, 7·7; N, 11·2%), and the *p-isomer* m. p. 142° (Found: C, 75·7; H, 7·0; N, 11·0%).

Hex-2-ene Nitrosate.—Nitric acid (35 c.c.) was added during 1½ hr. to hex-2-ene (20 g.) and pentyl nitrite (40 c.c.) at <0°. The liquid became blue, and slowly solidified. The crystals of *nitrosate* were removed and washed with alcohol till white (8 g.); they had m. p. 110° (decomp.) [Found: C, 41·3; H, 6·95; N, 15·9%; *M* (cryoscopic in benzene), 350·0; (cryoscopic in naphthalene), 195·4. $C_6H_{12}O_4N_2$ requires C, 40·9; H, 6·8; N, 15·9%; *M*, 176].

The other nitrosates were prepared in the above manner.

Hex-2-ene Nitrolpiperidide.—Prepared from hex-2-ene nitrosate (1 g.) and recrystallised from alcohol–water this *compound* (1·3 g.) had m. p. 94° (Found: C, 66·4; H, 11·0; N, 13·9. $C_{11}H_{22}ON_2$ requires C, 66·6; H, 11·1; N, 14·15%).

Hex-2-ene Nitrosochloride.—The nitrosochloride was obtained from the organic layer as a blue oil (2 g.), by drying ($CaCl_2$) and removal of other materials under reduced pressure. The oil decomposed on distillation, even under reduced pressure (Found: N, 8·9; Cl, 21·7. Calc. for $C_6H_{12}ONCl$: N, 9·4; Cl, 23·5%). On exposure to moist air it deposited crystals of hydroxylamine hydrochloride.

Hept-2-ene Nitrosochloride.—The nitrosochloride was obtained as an unstable blue oil (2 g.) (Found: N, 8·3; Cl, 19·85. Calc. for $C_7H_{14}ONCl$: N, 8·6; Cl, 21·7%).

Hept-2-ene Nitrosate.—The nitrosate was isolated as a blue-green oil (2 g.), which decomposed on distillation (Found: N, 13·8. Calc. for $C_7H_{14}O_4N_2$: N, 14·7%).

Oct-2-ene Nitrosochloride.—The nitrosochloride was isolated as an unstable blue oil (2 g.) (Found: N, 6·8; Cl, 18·5. Calc. for $C_8H_{16}ONCl$: N, 7·9; Cl, 20·0%).

Oct-2-ene Nitrosate.—The nitrosate was isolated as a blue-green unstable oil (2 g.) (Found: N, 12·8. Calc. for $C_8H_{16}O_4N_2$: N, 13·7%).

4-Methylpent-2-ene nitrosochloride (Found: N, 8·7; Cl, 21·7. Calc. for $C_6H_{12}ONCl$: N, 9·4; Cl, 23·5%) and nitrosate (Found: N, 14·5. Calc. for $C_6H_{12}O_4N_2$: N, 15·9%) were also unstable.

2 : 4 : 4-*Trimethylpent*-1-*ene nitrosochloride* was obtained as white crystals, m. p. 78° (from ethanol) [Found: C, 53·8; H, 8·9; N, 8·05; Cl, 20·2%; *M* (cryoscopic in benzene), 351; (cryoscopic in naphthalene), 186. $C_8H_{16}ONCl$ requires C, 54·1; H, 9·1; N, 7·9; Cl, 20·0%; *M*, 177·5].

Isomerisation of 2 : 4 : 4-*Trimethylpent*-1-*ene Nitrosochloride.*—A solution of this nitrosochloride (5 g.) in ethanol (50 c.c.) was heated carefully to the b. p. A vigorous reaction occurred, and the colour changed from blue to yellow. The alcohol was removed, and the solid was recrystallised from alcohol–water, giving colourless 2-*chloro*-2-*hydroxyimino*-2 : 4 : 4-*trimethylpentane* (4·5 g.), m. p. 134° (Found: C, 53·9; H, 9·1; N, 8·0; Cl, 19·8. $C_8H_{16}ONCl$ requires C, 54·1; H, 9·0; N, 7·9; Cl, 20·0%).

2 : 4 : 4-*Trimethylpent*-1-*ene Nitrolpiperidide.*—2 : 4 : 4-Trimethylpent-1-ene nitrosochloride (1 g.) gave this *compound* (0·8 g.), m. p. 92° (from alcohol–water) (Found: C, 69·2; H, 11·3; N, 12·2. $C_{13}H_{26}ON_2$ requires C, 69·0; H, 11·5; N, 12·4%).

2 : 4 : 4-*Trimethylpent*-2-*ene Nitrosochloride.*—The *nitrosochloride* was obtained as colourless crystals (21 g.), m. p. 113°, from ethanol [Found: C, 54·3; H, 9·1; N, 8·05; Cl, 19·8%; *M* (cryoscopic in benzene) 353·5; (cryoscopic in naphthalene), 192·3].

A solution of it (5 g.) in ethanol (50 c.c.) was heated and worked up as above, giving 2-*chloro*-3-*hydroxyimino*-2 : 4 : 4-*trimethylpentane* as an oil (4 g.), which decomposed on distillation (Found: C, 53·8; H, 9·2; N, 7·7; Cl, 19·6%).

2-*Hydroxy*-2 : 4 : 4-*trimethylpentan*-3-*one.*—2 : 4 : 4-Trimethylpent-2-ene nitrosochloride

(20 g.), hydrochloric acid (200 c.c.), water (200 c.c.), and ethanol (200 c.c.) were heated under reflux for 3 hr. Water (500 c.c.) was then added, and the whole was extracted six times with ether. The ethereal solution was dried (K_2CO_3) and distilled, giving the *ketol* (5 g.), b. p. 185—187° (Found: C, 66·0; H, 11·8. $C_9H_{16}O_2$ requires C, 66·7; H, 11·1%).

A sample with 2 : 4-dinitrophenylhydrazine in warm sulphuric acid–alcohol gave the *dinitrophenylhydrazone*, red needles (from ethanol), m. p. 230° (decomp.) (Found: C, 51·7; H, 6·2; N, 17·4. $C_{14}H_{20}O_5N_4$ requires C, 51·9; H, 6·2; N, 17·3%).

2 : 4 : 4-*Trimethylpent-2-ene Nitrolpiperidide*.—The nitrosochloride (1 g.) gave the *nitrolpiperidide* (1·2 g.), m. p. 112° (from alcohol–water) (Found: C, 69·1; H, 11·4; N, 11·9. $C_{13}H_{26}ON_2$ requires C, 69·0; H, 11·5; N, 12·4%).

2 : 4 : 4-*Trimethylpent-2-ene Nitrosate*.—The *nitrosate* was isolated as white crystals (17 g.), m. p. 124°, from ethanol [Found: C, 47·1; H, 7·8; N, 13·6%; *M* (cryoscopic in benzene), 406·5; (cryoscopic in naphthalene), 229·9. $C_8H_{16}O_4N_2$ requires C, 47·1; H, 7·8; N, 13·7%; *M*, 204].

Styrene Nitrosochloride.—This was isolated as white crystals, m. p. 103° (decomp.), from ethanol [Found: C, 56·65; H, 4·6; N, 8·15; Cl, 21·1%; *M* (cryoscopic in benzene), 343·0; (cryoscopic in naphthalene), 185·1. Calc. for C_8H_8ONCl: C, 56·6; H, 4·7; N, 8·3; Cl, 20·9%; *M*, 169·5].

Styrene nitrolpiperidide, recrystallised from alcohol–water, had m. p. 136° (Found: C, 71·6; H, 8·3; N, 13·1. $C_{13}H_{18}ON_2$ requires C, 71·55; H, 8·3; N, 12·8%).

Similarly were prepared: *α-methylstyrene nitrosochloride*, white crystals (22 g.), m. p. 90° (decomp.) (from ethanol) [Found: C, 58·4; H, 5·6; N, 7·8; Cl, 19·3%; *M* (cryoscopic in benzene), 370·5; (cryoscopic in naphthalene), 198·0. $C_9H_{10}ONCl$ requires C, 58·8; H, 5·45; N, 7·6; Cl, 19·3%; *M*, 183·5], and *nitrolpiperidide*, m. p. 123° (from ethanol) (Found: C, 72·4; H, 8·7; N, 11·9. $C_{14}H_{20}ON_2$ requires C, 72·4; H, 8·6; N, 12·1%); *2-methylstyrene nitrosochloride*, m. p. 98° (decomp.) (from ethanol) [Found: C, 58·8; H, 5·5; N, 7·8; Cl, 19·5%; *M* (cryoscopic in benzene), 370·9; (cryoscopic in naphthalene), 207·7. $C_9H_{10}ONCl$ requires C, 58·8; H, 5·45; N, 7·6; Cl, 19·3%; *M* 183·5], and *nitrolpiperidide*, m. p. 132° (from ethanol) (Found: C, 72·6; H, 8·8; N, 12·1. $C_{14}H_{20}ON_2$ requires C, 72·4; H, 8·6; N, 12·1%); the *3-methyl analogues*, m. p. 104° (decomp.) (from ethanol) [Found: C, 59·0; H, 5·5; N, 7·7; Cl, 19·2%; *M* (cryoscopic in benzene), 371·9; (cryoscopic in naphthalene), 215·7], and m. p. 138° (Found: C, 71·92; H, 8·69; N, 12·2%), respectively; the *4-methyl analogues*, m. p. 102° (decomp.) [Found: C, 59·0; H, 5·6; N, 7·7; Cl, 19·35%; *M* (cryoscopic in benzene), 358·2; (cryoscopic in naphthalene), 217·0], and m. p. 162° (Found: C, 72·5; H, 8·8; N, 11·9%), respectively; α : 4-*dimethylstyrene nitrosochloride*, m. p. 97° (from ethanol) [Found: C, 60·9; H, 6·1; N, 7·2; Cl, 18·1%; *M* (cryoscopic in benzene), 401·8; (cryoscopic in naphthalene), 210·5. $C_{10}H_{12}ONCl$ requires C, 60·75; H, 6·1; N, 7·1; Cl, 18·0%; *M*, 197·5], and *nitrolpiperidide*, m. p. 107° (from aqueous ethanol) (Found: C, 73·0; H, 8·9; N, 10·7. $C_{15}H_{22}ON_2$ requires C, 73·2; H, 8·9; N, 11·4%); *o-methoxypropenylbenzene nitrosochloride*, m. p. 124° (from alcohol) [Found: C, 56·0; H, 5·7; N, 6·45; Cl, 16·6%; *M* (cryoscopic in benzene), 425·8; (cryoscopic in naphthalene), 238·8. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·6; N, 6·6; Cl, 16·65%; *M*, 213·5], and m. p. 142° (Found: C, 68·6; H, 8·4; N, 10·8. $C_{15}H_{22}O_2N_2$ requires C, 68·7; H, 8·4; N, 10·7%); the *m-methoxy-analogues*, m. p. 134° (from ethanol) [Found: C, 56·4; H, 5·7; N, 6·7; Cl, 16·8%; *M* (cryoscopic in benzene), 432·7; (cryoscopic in naphthalene), 234·1], and *nitrolpiperidide*, m. p. 148° (from alcohol) (Found: C, 68·8; H, 8·5; N, 10·5%), respectively; and the *p-methoxy-analogues*, m. p. 126° (from ethanol) [Found: C, 56·1; H, 5·6; N, 6·6; Cl, 16·5%; *M* (cryoscopic in benzene), 431·7; (cryoscopic in naphthalene), 235·3], and m. p. 117° (Found: C, 68·9; H, 8·4; N, 10·4%), respectively.

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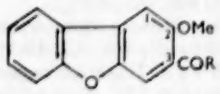
822. *Oxygen Heterocycles. Part VI.* Orientation in the Substitution of 2-Methoxydibenzofuran.*

By Cl. Routier, Ng. Ph. Buu-Hoï, and R. Royer.

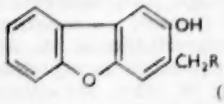
2-Methoxydibenzofuran undergoes Friedel–Crafts reactions with aliphatic acid chlorides and succinic anhydride at the 3-position, and with benzoyl chloride and phthalic anhydride at another position; formylation with dimethylformamide occurs at the 3-position. Many new dibenzofuran derivatives have been prepared.

The orientation in reactions with 2-methoxybenzofuran is of interest in view of the many possible sites for substitution. Gilman and Van Ess [1] found that bromination gave predominantly 3-bromo-2-methoxydibenzofuran, with traces of the 1-bromo-derivative, and Schimmelschmidt [2] found that nitration likewise occurs at the 3-position. No studies had yet been made of orientation in its Friedel–Crafts reactions.

Reaction of acetyl chloride with 2-methoxydibenzofuran in the presence of aluminium chloride in nitrobenzene yielded the 3-acetyl derivative (I; R = Me), whose structure was

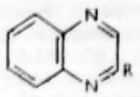


(I)



(II)

proved by conversion with sodium hypobromite into the known 3-carboxy-2-methoxydibenzofuran. Similarly, propionylation and butyrylation gave the 3-acyl compounds. Succinoylation with succinic anhydride afforded γ-(2-methoxy-3-dibenzofuryl)-γ-oxobutyric acid, whose constitution was established by decarboxylation to 2-methoxy-3-propionyldibenzofuran. The orientation was different in acylation with benzoyl chloride, even under the same experimental conditions, and an *x*-benzoyl-2-methoxydibenzofuran was obtained, which differed from the 3-benzoyl derivative (I; R = Ph) prepared by Friedel–Crafts reaction of the chloride of 2-methoxydibenzofuryl-3-carboxylic acid with



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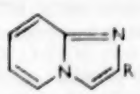
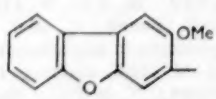
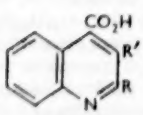


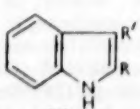
(IV)

R =





(V)



(VI)

benzene. Phthaloylation with phthalic anhydride gave a keto-acid which was decarboxylated to a ketone identical with the product of direct benzoylation of 2-methoxydibenzofuran. The dissimilar behaviour of aliphatic and aromatic acid chlorides and anhydrides is reminiscent of the acylation of 2-methoxynaphthalene.[3]

2-Methoxydibenzofuran with dimethylformamide in the presence of phosphorus oxychloride gave 3-formyl-2-methoxydibenzofuran (I; R = H); its oxime was dehydrated

* Part V, Lescot, Buu-Hoï, and Xuong, *J.*, 1956, 2408.

[1] Gilman and van Ess, *J. Amer. Chem. Soc.*, 1939, **61**, 1365.

[2] Schimmelschmidt, *Annalen*, 1950, **566**, 184.

[3] Cf. Fierz-David and Jaccard, *Helv. Chim. Acta*, 1928, **11**, 1042; Haworth and Sheldrick, *J.*, 1934, 864.

with acetic anhydride to a nitrile identical with that prepared [4] by a Sandmeyer reaction from 3-amino-3-methoxydibenzofuran.

Wolff–Kishner–Huang-Minlon reduction [5] of 3-acetyl- and 3-propionyl-2-methoxydibenzofuran readily afforded the 3-ethyl- and the 3-*n*-propyl-compound, whose demethylation with pyridine hydrochloride yielded 3-ethyl-2-hydroxy- (II; R = Me) and 2-hydroxy-3-*n*-propyl-dibenzofuran (II; R = Et). γ-(2-Methoxy-3-dibenzofuryl)-γ-oxobutyric acid was also reduced to γ-3-(2-methoxydibenzofuryl)butyric acid, but reduction of 3-butyryl-2-methoxydibenzofuran under the same conditions was accompanied by complete demethylation, to 3-*n*-butyl-2-hydroxydibenzofuran (II; R = Pr^n).

The preferential homonuclear 3-substitution in 2-methoxybenzofuran brought to light is in line with recent observations on similar nuclei such as carbazole or dibenzoselenophen.[6] 3-Acetyl-2-methoxydibenzofuran was brominated in the side chain, as shown by the formation of a quaternary picolinium salt; [7] further, 3-bromoacetyl-2-methoxydibenzofuran with *o*-phenylenediamine [8] gave the quinoxaline (III), and with 2-aminopyridine [9] the hydrobromide of the glyoxalinopyridine (IV).

The use of 3-acyl-2-methoxydibenzofurans for the preparation of various nitrogen-containing heterocycles was investigated. Pfitzinger reactions with isatin gave an interesting example of steric hindrance,[10] 3-acetyl-2-methoxydibenzofuran affording a 40% yield of the corresponding cinchoninic acid (V; R′ = H) after 75 hours' heating, whereas the higher homologue (I; R = Et) gave only 10% of the acid (V; R′ = Me) after 100 hours' heating, and the next higher homologue (I; R = Pr) gave no trace of the cinchoninic acid even after 150 hours. In the indole series, 2-(2-methoxy-3-dibenzofuryl)indole (VI; R′ = H) and the 3-ethyl homologue (VI; R′ = Et) were obtained by Fischer cyclisation of phenylhydrazones of the appropriate ketones; demethylation with pyridine hydrochloride gave the corresponding phenolic indoles.

Experimental

3-Acetyl-2-methoxydibenzofuran (I; R = Me).—To an ice-cooled, stirred solution of 2-methoxydibenzofuran (45 g.; prepared by methylation of the hydroxy-compound with aqueous sodium hydroxide and dimethyl sulphate) and acetyl chloride (20 g.) in dry nitrobenzene (150 c.c.), finely powdered aluminium chloride (35 g.) was added in small portions; after 14 hr. at room temperature, the mixture was poured into water, and the nitrobenzene removed in steam. Benzene was added, the benzene solution washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvent removed, and the residue distilled *in vacuo*. The *ketone* (42 g.) formed colourless prisms, m. p. 125°, from *cyclo*hexane, giving a yellow halochromy in sulphuric acid (Found: C, 74·9; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

2-Methoxydibenzofuran-3-carboxylic Acid.—A solution of the foregoing ketone (20 g.) in dioxan (200 c.c.) was shaken for 4 hr. at room temperature with aqueous sodium hypobromite prepared from bromine (12 c.c.) and sodium hydroxide (25 g. in 100 c.c. of water). The aqueous layer was decanted off, treated with aqueous sodium hydrogen sulphite, concentrated *in vacuo*, filtered, and acidified with hydrochloric acid. The precipitated acid (10 g.) formed colourless needles, m. p. 207°, from benzene (Found: C, 69·5; H 4·0. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·1%). Gilman and van Ess [1] gave m. p. 206—207° for the acid prepared by a Grignard reaction with 3-bromo-2-methoxydibenzofuran and carbon dioxide.

3-Ethyl-2-methoxydibenzofuran.—A mixture of 3-acetyl-2-methoxydibenzofuran (10 g.), 98% hydrazine hydrate (3 g.), and diethylene glycol (200 c.c.) was heated for 10 min., and after addition of potassium hydroxide (3 g.), refluxed for 2 hr. with removal of water. After cooling and dilution with water, the product was taken up in ether and purified by distillation *in vacuo*, to give a *product* (7 g.), b. p. 197—200°/12 mm., forming colourless leaflets, m. p. 48°, from aqueous ethanol (Found: C, 79·6; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%).

[4] Moualin and Venkataraman, *J. Sci. Ind. Res., India*, 1945, **3**, 447.
[5] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **67**, 2478.
[6] Sawicki, *J. Amer. Chem. Soc.*, 1954, **76**, 664; *J. Org. Chem.*, 1954, **19**, 608.
[7] Tschitschibabin, *Ber.*, 1927, **60**, 1607.
[8] Hinsberg, *Annalen*, 1896, **292**, 246; Buu-Hoï and Khôi, *Bull. Soc. chim. France*, 1950, **17**, 753; Buu-Hoï, Lavit, and Xuong, *J. Org. Chem.*, 1954, **19**, 1617.
[9] Tschitschibabin *et al.*, *Ber.*, 1925, **58**, 1704; 1926, **59**, 2048; 1931, **64**, 2842.
[10] Buu-Hoï, Royer, Xuong, and Jacquignon, *J. Org. Chem.*, 1953, **18**, 1209; Buu-Hoï and Cagniant, *Bull. Soc. chim. France*, 1946, **13**, 123.

3-*Ethyl*-2-*hydroxydibenzofuran* (II; R = Me).—A mixture of the foregoing ether (6 g.) and pyridine hydrochloride (6 g.) was gently refluxed for 30 min., and water added after cooling; the precipitate (5 g.) formed long, colourless needles, m. p. 109—110°, from aqueous ethanol (Found: C, 79·3; H, 5·6. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%).

2-*Methoxy*-3-*propionyldibenzofuran* (I; R = Et).—This *ketone* (21·5 g.), prepared from 2-methoxydibenzofuran (20 g.), propionyl chloride (11 g.), and aluminium chloride (16 g.) as for the lower homologue, crystallised as prisms, b. p. 238°/12 mm., m. p. 123°, from *cyclo*hexane (Found: C, 75·5; H, 5·4. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%). Reduction of this ketone (10 g.) with hydrazine hydrate afforded 2-*methoxy*-3-n-*propyldibenzofuran* (7·5 g.), b. p. 220—222°/12 mm., forming plates, m. p. 44°, from light petroleum (b. p. 35—45°) (Found: C, 80·3; H, 6·5. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%); demethylation of this ether (4 g.) with pyridine hydrochloride (4 g.) gave 2-*hydroxy*-3-n-*propyldibenzofuran* (3·5 g.), crystallising as needles, m. p. 103—104°, from aqueous ethanol (Found: C, 79·9; H, 6·2. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%).

3-n-*Butyryl*-2-*methoxydibenzofuran* (I; R = Pr^n).—This *ketone* (11·5 g.), prepared from 2-methoxydibenzofuran (10 g.), *n*-butyryl chloride (7 g.), and aluminium chloride (8 g.), formed needles, m. p. 123°, b. p. 245—247°/12 mm., from *cyclo*hexane (Found: C, 76·3; H, 6·0. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%). Its reduction was accompanied by demethylation and gave 3-n-*butyl*-2-*hydroxydibenzofuran* (II; R = Pr), prisms, m. p. 101° (from aqueous ethanol) (Found: C, 80·2; H, 6·6. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%).

γ-(2-*Methoxy*-3-*dibenzofuryl*)-γ-*oxobutyric Acid*.—Into an ice-cooled suspension of 2-methoxydibenzofuran (21 g.) and succinic anhydride (13 g.) in nitrobenzene (150 c.c.), aluminium chloride (17 g.) was stirred in small portions; after 12 hr. at room temperature, followed by 15 min. at 50—60°, the mixture was poured on ice, the nitrobenzene removed in steam, and the *keto-acid* purified *via* its sodium salt. After recrystallisation, first from aqueous acetic acid, then from benzene, it formed prisms (20 g.), m. p. 195—196° (Found: C, 68·3; H, 4·4. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). Reduction of this acid (13·5 g.) with hydrazine hydrate (9 g.) and potassium hydroxide (9 g.) in diethylene glycol (200 c.c.) afforded γ-(2-*methoxy*-3-*dibenzofuryl*)*butyric acid* (7 g.), m. p. 59—60° (from light petroleum) (Found: C, 71·6; H, 5·5. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%).

3-*Benzoyl*-2-*methoxydibenzofuran* (I; R = Ph).—2-Methoxydibenzofuran-3-carboxylic acid (7 g.; prepared by dimethylation of commercial 2-hydroxy-3-acid with aqueous sodium hydroxide and dimethyl sulphate, and subsequent saponification of methyl 2-methoxydibenzofuran-3-carboxylate) was converted by thionyl chloride into its solid chloride; a solution of this in dry benzene (200 c.c.) was treated with aluminium chloride (5 g.), and the mixture kept for 12 hr. at room temperature, refluxed for 1 hr., then worked up in the usual way. The *ketone* (3 g.) formed colourless prisms, m. p. 133—134°, from *cyclo*hexane (Found: C, 79·2; H, 4·4. $C_{20}H_{14}O_3$ requires C, 79·5; H, 4·7%).

x-*Benzoyl*-2-*methoxydibenzofuran*.—To a water-cooled solution of 2-methoxydibenzofuran (8 g.) and benzoyl chloride (6 g.) in dry nitrobenzene (100 c.c.), aluminium chloride (5 g.) was added in small portions with stirring, and the mixture left for 14 hr. at room temperature, then worked up in the usual way. The *ketone* (7 g.) obtained, b. p. 270—275°/12 mm., crystallised from *cyclo*hexane, as needles, m. p. 124°, whose solutions in sulphuric acid were yellow (Found: C, 79·4; H, 4·8%). The m. p. was strongly depressed on admixture with 3-benzoyl-2-methoxydibenzofuran. The most probable positions entered by the benzoyl substituent are positions 1 or 8.

x-o-*Carboxybenzoyl*-2-*methoxydibenzofuran*.—This *compound* (11 g.), prepared from phthalic anhydride (9 g.), 2-methoxydibenzofuran (10 g.), and aluminium chloride (9 g.) in nitrobenzene (150 c.c.) as for the succinoylation, crystallised as colourless, sublimable needles, m. p. 236° (Found: C, 72·5; H, 3·9. $C_{21}H_{14}O_5$ requires C, 72·8; H, 4·1%). Heating of a mixture of it with lime gave a ketone, which melted at 124°, alone or mixed with the foregoing *x*-benzoyl-2-methoxydibenzofuran.

3-*Formyl*-2-*methoxydibenzofuran* (I; R = H).—A mixture of 2-methoxydibenzofuran (19·5 g.), dimethylformamide (10 g.), and phosphorus oxychloride (20 g.) was cautiously heated until a reaction set in; the mixture, which became brown, was then heated for a further 6 hr. on a water-bath, and, after addition of saturated aqueous sodium acetate in excess and further refluxing for a few min., the product was taken up in chloroform and fractionated *in vacuo*. The *aldehyde* (5·5 g.), b. p. 237—240°/12 mm., formed needles, m. p. 165°, from *cyclo*hexane, giving an orange halochromy in sulphuric acid (Found: C, 74·6; H, 4·7. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·5%). The corresponding *aldoxime* crystallised as prisms, m. p. 199—200°, from

aqueous ethanol (Found : N, 5·7. $C_{14}H_{11}O_3N$ requires N, 5·8%). A solution of this oxime (2 g.) in acetic anhydride (150 c.c.) was refluxed for 5 hr., and then treated with dilute aqueous sodium hydroxide; the precipitate was collected and crystallised from methanol, giving 3-cyano-2-methoxydibenzofuran, colourless, sublimable needles, m. p. 208° (lit.,[4] m. p. 200°) (Found : N, 6·0. Calc. for $C_{14}H_9O_2N$: N, 6·2%). Hydrolysis of this nitrile with sodium hydroxide in ethanol yielded 2-methoxydibenzofuran-3-carboxylic acid, m. p. 207° alone or mixed with a sample prepared from 2-hydroxydibenzofuran-3-carboxylic acid.

3-Bromoacetyl-2-methoxydibenzofuran.—To a solution of 3-acetyl-2-methoxydibenzofuran (9 g.) in acetic acid (200 c.c.), bromine (7 g.) was added dropwise with stirring, and the mixture left for 5 hr. until dissolution occurred, then poured into water. The precipitate was collected, washed with water, and crystallised from ethanol, giving cream-coloured needles (7 g.), m. p. 164—165° (Found : C, 56·3; H, 3·5. $C_{15}H_{11}O_3Br$ requires C, 56·4; H, 3·4%). The corresponding quaternary *2-picolinium bromide*, prepared by refluxing for 2 hr. a solution in ethanol (20 c.c.) of this bromo-ketone (2 g.) and α-picoline (0·6 g.), crystallised as large, colourless prisms, m. p. 256—257° (decomp.), from aqueous ethanol (Found : N, 3·6. $C_{21}H_{18}O_2NBr$ requires N, 3·4%); treatment of a boiling aqueous solution of this salt (1 g.) with sodium hydrogen carbonate (5 g.) yielded *2-(2-methoxy-3-dibenzofuryl)pyrrocoline* (0·5 g.), forming yellowish needles, m. p. 134°, from ethanol (Found : N, 4·2. $C_{21}H_{15}O_2N$ requires N, 4·4%).

2-(2-Methoxy-3-dibenzofuryl)quinoxaline (III).—A mixture of the foregoing ω-bromo-ketone (1 g.), *o*-phenylenediamine (0·4 g.), and sodium acetate (0·5 g.) in ethanol (150 c.c.) was refluxed for 5 hr., water was added, and the precipitate collected and recrystallised from ethanol, giving yellowish needles, m. p. 92—93° (Found : N, 8·3. $C_{21}H_{14}O_2N_2$ requires N, 8·6%).

4-(2-Methoxy-3-dibenzofuryl)pyridino(1′ : 2′-1 : 2)glyoxaline Hydrobromide.—A mixture of the bromo-ketone (1 g.) and 2-aminopyridine (0·3 g.) in ethanol (15 c.c.) was refluxed for 12 hr. The *salt* precipitated on cooling formed fine, yellowish prisms (0·6 g.), m. p. 310° (decomp.), from ethanol (Found : N, 7·0; Br, 20·0. $C_{20}H_{15}O_2N_3Br$ requires N, 7·1; Br, 20·3%).

2-(2-Methoxy-3-dibenzofuryl)indole (VI; R = H).—A mixture of 3-acetyl-2-methoxydibenzofuran (5 g.) and phenylhydrazine (2·5 g.) was heated for 15 min. at 120° with removal of water; finely powdered anhydrous zinc chloride (5 g.) was then added, and heating renewed at 180° for 20 min. After cooling, dilute aqueous acetic acid was added; the product was then taken up in benzene, the benzene solution washed with water and dried (Na_2SO_4), the solvent distilled off, and the solid residue recrystallised from ethanol (charcoal), giving long, colourless needles, m. p. 168° (Found : C, 80·2; H, 5·0; N, 4·6. $C_{21}H_{15}O_2N$ requires C, 80·5; H, 4·8; N, 4·5%). It gave benzene solutions with a strong violet fluorescence, and a brown picrate.

2-(2-Hydroxy-3-dibenzofuryl)indole.—A mixture of the foregoing indole (2 g.) and redistilled pyridine hydrochloride (6 g.) was refluxed for 15 min., and water was added after cooling. The precipitate formed was converted into the sodium salt, which formed yellowish leaflets from hot water. Decomposition of this salt with aqueous acetic acid gave an *indole*, crystallising as yellowish, oxidisable prisms (1 g.), m. p. 234—235° (decomp.) (Found : N, 4·9. $C_{20}H_{13}O_2N$ requires N, 4·7%).

3-Ethyl-2-(2-methoxy-3-dibenzofuryl)indole (VI; R = Et).—Prepared from 3-*n*-butyryl-2-methoxydibenzofuran (5 g.), phenylhydrazine (2 g.), and zinc chloride (5 g.) as for the lower homologue, this *indole* (2 g.) formed yellowish prisms, m. p. 150°, from ethanol (Found : C, 80·6; H, 5·4. $C_{23}H_{19}O_2N$ requires C, 80·9; H, 5·6%). *3-Ethyl-2-(2-hydroxy-3-dibenzofuryl)indole* formed yellowish, oxidisable prisms, m. p. 191° (decomp.), from benzene (Found : N, 4·0. $C_{22}H_{17}O_2N$ requires N, 4·3%).

2-(2-Methoxy-3-dibenzofuryl)cinchoninic Acid (V; R′ = H).—A solution of isatin (2·6 g.), 3-acetyl-2-methoxydibenzofuran (5 g.), and ethanol (50 c.c.) was refluxed with potassium hydroxide (3·5 g.; dissolved in the minimum of water) for 75 hr.; the mixture was diluted with water, the neutral impurities removed by ether-extraction, and the aqueous layer acidified with acetic acid. The precipitate formed fine, yellowish prisms (3·2 g.), subliming above 230°, m. p. 260°, from aqueous acetic acid (Found : C, 74·5; H, 4·0; N, 3·9. $C_{23}H_{15}O_4N$ requires C, 74·8; H, 4·1; N, 3·8%). Thermal decarboxylation of this acid gave *2-(2-methoxy-3-dibenzofuryl)quinoline*, forming pale yellow needles, m. p. 175°, from ethanol (Found : N, 4·4. $C_{22}H_{15}O_2N$ requires N, 4·3%).

2-(2-Methoxy-3-dibenzofuryl)-3-methylcinchoninic Acid (V; R′ = Me).—This *acid* (0·3 g.), obtained after 100 hours' refluxing, formed fine, yellowish prisms, m. p. 317—318°, from aqueous acetic acid (Found : C, 75·0; H, 4·5; N, 3·6. $C_{24}H_{17}O_4N$ requires C, 75·2; H, 4·5; N, 3·7%).

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823. *Application of the Bruckner Method to the Synthesis of Phenanthridine Derivatives.*

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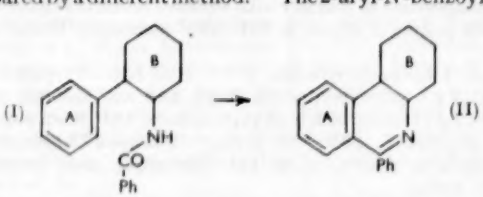
1-Aryl*cyclo*hexenes have been converted into 1-aryl-2-nitro*cyclo*hexenes and compounds regarded as 1-aryl-2-nitro-1-nitroso*cyclo*hexanes. *cis*-2-Aryl*cyclo*hexylamines are obtained by reduction of the 1-aryl-2-nitro*cyclo*hexenes, and their benzoates are cyclised to 1 : 2 : 3 : 4 : 4*a* : 10*a*-hexahydrophenanthridines. 6-Methoxy-9-phenylphenanthridine is formed readily by dehydrogenation of the corresponding hexahydro-compound. *N*-Benzoyl-2-phenyl*cyclo*pentylamine is prepared by the same route and cyclised to 3 : 4-dihydro-1-phenyl*cyclo*penta[*c*]*iso*quinoline.

Bruckner and his co-workers [1] synthesised 3-methyl*iso*quinolines by a method in which addition of dinitrogen trioxide to 1-arylpropenes is the first step. We report here our extension of this method to the synthesis of phenanthridine derivatives by the use of 1-aryl*cyclo*hexenes in place of 1-arylpropenes.

Addition of dinitrogen trioxide to 1-phenyl*cyclo*hexene yields, according to the conditions, predominantly either 1-nitro-2-phenyl*cyclo*hexene or a compound, m. p. 224° (decomp.), regarded as 2-nitro-1-nitroso-1-phenyl*cyclo*hexane.* The latter gave in cold alcoholic alkali a deep red solution from which the original nitrosite was recovered by acidification. It was unchanged by acetic anhydride–sulphuric acid under conditions which convert 1-arylpropene nitrosites into 1-aryl-2-nitropropyl acetates.[1] With acetic anhydride in pyridine, the acetate of the *aci*-form of the nitrosite was formed, which regenerated the original substance on hydrolysis with alcoholic alkali. Oxidation of the nitrosite with potassium permanganate gave benzoic acid. 1-*o*-, 1-*m*-, and 1-*p*-Tolyl-, and 1-*m*-methoxphenyl-*cyclo*hexene similarly gave 1-aryl-2-nitro*cyclo*hexenes or solid nitrosites. 1-Aryl*cyclo*hexanols were formed in all cases by concomitant hydration, and in some cases could not be eliminated from the 1-aryl-2-nitro*cyclo*hexenes.

The 1-aryl-2-nitro*cyclo*hexenes were reduced in good yields to *cis*-2-aryl*cyclo*hexylamines by lithium aluminium hydride. Heating the benzamide derived from 1-nitro-2-phenyl-*cyclo*hexene with palladised charcoal in *p*-cymene gave 2-benzamidodiphenyl and *N*-benzoyl-*trans*-2-phenyl*cyclo*hexylamine.[2] The m. p. of the *N*-phenylthioureide of the amine was in agreement with that reported for the *N*-phenylthioureide of *cis*-2-phenyl-*cyclo*hexylamine prepared by a different method.[3] The 2-aryl-*N*-benzoyl*cyclo*hexylamines (I)



were cyclised to 1 : 2 : 3 : 4 : 4*a* : 10*a*-hexahydrophenanthridines (II) by phosphoric oxide–phosphorus oxychloride : [4] good yields were obtained from the benzoyl derivatives of 2-*m*-tolyl- and 2-*m*-methoxyphenyl-*cyclo*hexylamine; in the other cases, since ring B is alicyclic and there is no activation, the poor yields realised were to be expected. As a test case, the dehydrogenation of 1 : 2 : 3 : 4 : 4*a* : 10*a*-hexahydro-6-methoxy-9-phenylphenanthridine was found to proceed readily with palladised charcoal, yielding 6-methoxy-9-phenylphenanthridine.

* Part of this work was published in *Chem. and Ind.*, 1954, 757.

[1] Bruckner, *Annalen*, 1935, **518**, 227; Bruckner and Kramli, *J. prakt. Chem.*, 1936, **145**, 291; Bruckner, Fodor, Kiss, and Kovacs, *J.*, 1948, 885; Bruckner and Fodor, *Ber.*, 1943, **76**, 466.

[2] Nightingale and Tweedie, *J. Amer. Chem. Soc.*, 1944, **66**, 1963.

[3] Arnold and Richardson, *ibid.*, 1954, **76**, 3649.

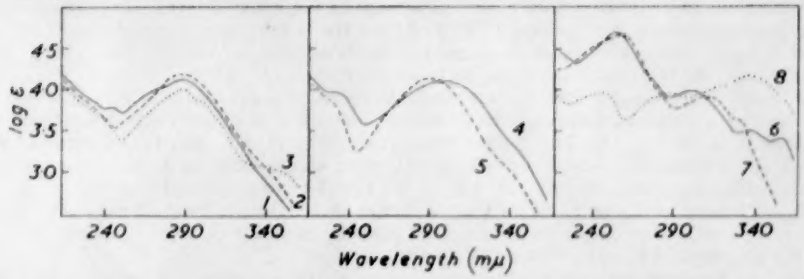
[4] Whaley and Hartung, *J. Org. Chem.*, 1949, **14**, 650.

Under conditions employed for the preparation of 1-aryl-2-nitro*cyclo*hexenes, 1-nitro-2-phenyl*cyclo*pentene and 1-nitro-2-phenyl*cyclo*heptene were obtained from 1-phenyl*cyclo*pentene and 1-phenyl*cyclo*heptene respectively. 2-Phenyl*cyclo*pentylamine was prepared by lithium aluminium hydride reduction of the nitro-compound, and its benzoyl derivative was cyclised to **3 : 4-dihydro-1-phenyl*cyclo*penta[*c*]*iso*quinoline**. The ultraviolet absorption spectra of the cyclised bases and of 6-methoxy-9-phenylphenathridine are presented in the Figures.

Experimental

Addition of Dinitrogen Trioxide to 1-*Phenyl*cyclo*hexene*.—(*a*) A saturated aqueous solution (50 ml.) of sodium nitrite and ether (50 ml.) containing 1-phenyl*cyclo*hexene [5] (2 g.), cooled by ice-water, were treated with 4N-sulphuric acid at such a rate as to maintain continuous evolution of nitrous fumes.. The ethereal layer developed an intense blue colour which faded to light yellow in 2 hr., indicating completion of reaction. The ethereal layer was *immediately* separated, washed with water, and dried (Na_2SO_4). The combined ether extracts from 20 such experiments

Absorption spectra of (1) **3 : 4-*dihydro*-4-*methyl*-1-*phenyl*isoquinoline *hydrochloride*,** (2) **1 : 2 : 3 : 4 : 4a : 10a-*hexahydro*-9-*phenyl*-**, (3) **-7-*methyl*-9-*phenyl*-, *and*** (4) **-6(8)-*methyl*-9-*phenyl*-*phenanthridine hydrochloride*,** (5) **3 : 4-*dihydro*-1-*phenyl*cyclo*penta*[c]isoquinoline *hydrochloride*,** (6) **9-*phenyl*- *and*** (7) **6-*methoxy*-9-*phenyl*-*phenanthridine*,** (8) **1 : 2 : 3 : 4 : 4a : 10a-*hexahydro*-6-*methoxy*-9-*phenyl*phenanthridine *hydrochloride*** (*all in* EtOH).



were treated with sodium (10 g.) in methanol (150 ml.) with vigorous shaking. Water (150 ml.) was added to the solution with stirring and the deep red aqueous layer separated. The ethereal layer was repeatedly washed with dilute aqueous sodium hydroxide, till the aqueous layer was no longer coloured, dried (Na_2SO_4), and evaporated. Two distillations of the residual oil in a vacuum gave 1-phenyl*cyclo*hexanol (4 g.), b. p. 90—95°/3 mm., m. p. and mixed m. p. 62°, and 1-*nitro*-2-*phenyl*cyclo*hexene* (25 g.), b. p. 145—150°/3 mm. (Found : C, 72·3; H, 7·3; N, 7·4. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%). The alkaline extract was cooled and acidified with concentrated hydrochloric acid, to yield 2-*nitro*-1-*nitroso*-1-*phenyl*cyclo*hexane* (7 g.), yellow needles (from methanol), m. p. 224° (decomp.) (Found : C, 61·5; H, 6·2; N, 11·8. $C_{12}H_{14}O_3N_2$ requires C, 61·6; H, 6·0; N, 12·0%).

(*b*) An ice-cooled mixture of saturated aqueous sodium nitrite (50 ml.) and ether (50 ml.) containing 1-phenyl*cyclo*hexene (2 g.) was treated with 4N-sulphuric acid gradually till the initial blue colour faded to yellow, then the whole was set aside with periodical addition of dilute sulphuric acid, for 6 hr. The combined ether layers from 20 such experiments were worked up as previously. Very little 1-nitro-2-phenyl*cyclo*hexene was obtained. The main product was 2-nitro-1-nitroso-1-phenyl*cyclo*hexane (40 g.), m. p. and mixed m. p. 224° (decomp.). The *acetyl derivative*, obtained with acetic anhydride in pyridine at 100°, crystallised from methanol in colourless needles, m. p. 102—103° (Found : C, 61·0; H, 5·4; N, 9·8. $C_{14}H_{16}O_4N_2$ requires C, 60·9; H, 5·8; N, 10·2%).

cis-2-*Phenyl*cyclo*hexylamine*.—To a stirred solution of lithium aluminium hydride (12 g.) in ether (200 ml.) was added gradually a solution of 1-nitro-2-phenyl*cyclo*hexene (20 g.) in ether (200 ml.). The mixture was left at 30° for 24 hr., then decomposed by water. The ether layer was decanted and extracted repeatedly with 2N-hydrochloric acid (ether layer A). The combined acid extracts were cooled strongly, made alkaline with concentrated aqueous ammonia,

[5] Nametkin and Iwanoff, *Ber.*, 1923, **56**, 1805.

and extracted with ether. The extract on evaporation left 2-*phenyl*cyclo*hexylamine* (9 g.), b. p. 90°/0·3 mm. The *benzoyl derivative* (Schotten–Baumann method), crystallised from light petroleum, had m. p. 122—123° (Found: C, 81·9; H, 7·2; N, 4·7. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5; N, 5·0%). The *N*-phenylthioureide melted at 138° (Arnold and Richardson [5] reported m. p. 137—138°).

The ether layer A on evaporation gave a gummy *substance* (1·5 g.), which crystallised from alcohol as colourless needles, m. p. 153—155° (Found: C, 75·8; H, 8·1; N, 7·5. $C_{12}H_{15}ON$ requires C, 76·2; H, 7·9; N, 7·4%).

Dehydrogenation of N-*Benzoyl*-cis-2-*phenyl*cyclo*hexylamine*.—The benzamide (1 g.) was dehydrogenated with 15% palladised charcoal (0·4 g.) in *p*-cymene (50 ml.); 150 ml. of hydrogen were evolved (60% dehydrogenation). The solution was cooled and filtered. The residue was extracted with hot benzene and filtered. Evaporation of the filtrate left *N*-benzoyl-*trans*-2-phenyl*cyclo*hexylamine [6] (0·2 g.), which crystallised from benzene in feathery needles, m. p. and mixed m. p. 178° (Found: C, 82·1; H, 7·7; N, 5·2. Calc. for $C_{19}H_{21}ON$: C, 81·7; H, 7·5; N, 5·0%). The *p*-cymene filtrate was evaporated and the residue dissolved in benzene. Addition of light petroleum to turbidity gave more (0·1 g.) of the benzamide, m. p. 178°. The mother-liquor on evaporation gave a solid (0·4 g.), m. p. 80—85°, raised by chromatography to 83—85°, mixed m. p. with 2-benzamidodiphenyl,[6] 84—85°.

1 : 2 : 3 : 4 : 4a : 10a-*Hexahydro*-9-*phenylphenanthridine*.—A mixture of *N*-benzoyl-*cis*-2-phenyl*cyclo*hexylamine (3 g.) in xylene (75 ml.), phosphorus oxychloride (15 ml.), and phosphoric oxide (15 g.) was refluxed for 3 hr., cooled, and decomposed with ice. The aqueous layer was made alkaline and extracted with ether. The base in the ethereal layer was purified by one more passage through acid, to give 1 : 2 : 3 : 4 : 4*a* : 10*a*-hexahydro-9-phenylphenanthridine as an oil (0·3 g.). The *hydrochloride* crystallised from dry acetone as colourless plates, m. p. 240—241° (Found: C, 76·4; H, 6·4. $C_{19}H_{20}NCl$ requires C, 76·6; H, 6·7%).

Addition of Dinitrogen Trioxide to 1-m-*Methoxyphenyl*cyclo*hexene*.—The cyclo*hexene* was prepared by a Grignard reaction with *cyclo*hexanone and subsequent dehydration with 50% sulphuric acid; it had b. p. 120°/5 mm. (Found: C, 82·4; H, 8·1. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%). Treatment of the olefin (40 g.) with dinitrogen trioxide as in (*a*) above gave 1-m-*methoxyphenyl*-2-*nitro*cyclo*hexene* (28 g.), b. p. 130°/0·1 mm. (Found: C, 66·5; H, 6·6. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4%), and 1-m-*methoxyphenyl*-2-*nitro*-1-*nitroso*cyclo*hexane* (7 g.), yellow needles (from methanol), m. p. 161° (Found: C, 59·0; H, 6·0; N, 10·6. $C_{13}H_{16}O_4N_2$ requires C, 58·6; H, 5·5; N, 10·6%).

cis-2-m-*Methoxyphenyl*cyclo*hexylamine*.—Reduction of the foregoing nitro-olefin (25 g.) by lithium aluminium hydride gave the *cyclo*hexylamine (11 g.), b. p. 112—115°/3 mm., characterised as the *benzoyl derivative*, m. p. 165—168° (from ether) (Found: C, 78·2; H, 7·8; N, 4·9. $C_{20}H_{23}O_2N$ requires C, 77·7; H, 7·4; N, 4·5%). The neutral *substance* (0·8 g.) obtained in the reduction crystallised from alcohol, then having m. p. 154° (Found: C, 77·5; H, 8·0; N, 7·4. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

1 : 2 : 3 : 4 : 4a : 10a-*Hexahydro*-6-*methoxy*-9-*phenylphenanthridine*.—Cyclisation of the above benzoyl derivative (3·3 g.) in xylene (25 ml.) by phosphorus oxychloride (10 ml.) and phosphoric oxide (10 g.) gave the phenanthridine as an oil (1·95 g.). The *hydrochloride* crystallised from acetone–ether in colourless needles, m. p. 189° (decomp.) (Found: C, 73·1; H, 6·2. $C_{20}H_{22}ONCl$ requires C, 73·3; H, 6·7%).

6-*Methoxy*-9-*phenylphenanthridine*.—The above hexahydrophenanthridine (0·35 g.) was dehydrogenated in *p*-cymene (20 ml.) by 50% palladised charcoal (0·2 g.) during 8 hr. The solution was filtered and extracted with dilute hydrochloric acid. Basification of the extract and crystallisation of the precipitate from dilute alcohol gave the *phenanthridine*, m. p. 100—101° (Found: C, 83·9; H, 5·7. $C_{20}H_{15}ON$ requires C, 84·2; H, 5·3%).

Addition of Dinitrogen Trioxide to 1-o-*Tolyl*cyclo*hexene*.—Treatment of the olefin [7] (40 g.) with nitrous fumes according to procedure (*a*) above gave 1-*nitro*-2-o-*tolyl*cyclo*hexene* (30 g.), b. p. 128°/0·3 mm. (Found: C, 73·4; H, 7·1. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9%), and by procedure (*b*) 2-*nitro*-1-*nitroso*-1-o-*tolyl*cyclo*hexane* (35 g.), yellow needles (from methanol), m. p. 210° (decomp.) (Found: C, 63·1; H, 5·9. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·5%). The *acetyl derivative*, prepared by acetic anhydride and sulphuric acid and crystallised from methanol, had m. p. 99° (Found: C, 62·7; H, 5·7; N, 10·2. $C_{15}H_{18}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·7%).

[6] Pictet and Hubert, *Ber.*, 1896, **29**, 1186.
[7] Sherwood, Short, and Stansfield, *J.*, 1932, 1832.

cis-2-o-*Tolyl*cyclo*hexylamine*.—Reduction of the preceding nitro-olefin (25 g.) as above gave the amine (13 g.), b. p. 95—100°/0·5 mm., whose *benzoyl derivative* had m. p. 127—129° (from ether) (Found : C, 82·3; H, 8·1; N, 5·2. $C_{20}H_{23}ON$ requires C, 81·9; H, 7·9; N, 4·8%). The neutral *substance* (0·8 g.) obtained crystallised from alcohol in colourless needles, m. p. 172—174° (Found : C, 77·4; H, 8·2; N, 7·1. $C_{13}H_{17}ON$ requires C, 76·9; H, 8·4; N, 6·9%).

1 : 2 : 3 : 4 : 4a : 10a-*Hexahydro-5-methyl-9-phenylphenanthridine*.—The above benzoyl derivative (3·1 g.), by the usual procedure, yielded the phenanthridine (0·45 g.) whose *picrate* crystallised from alcohol in greenish-yellow plates, m. p. 186—187° after sintering at 176° (Found : C, 62·4; H, 5·1. $C_{26}H_{24}O_7N_4$ requires C, 61·9; H, 4·8%).

Addition of Dinitrogen Trioxide to 1-m-*Tolyl*cyclo*hexene*.—Treatment of the *cyclo*hexene [7] (40 g.) with dinitrogen trioxide according to procedure (*a*) gave 1-*nitro*-2-m-*tolyl*cyclo*hexene* (28 g.), b. p. 138—140°/0·5 mm. (Found : C, 74·2; H, 7·4%), and 2-*nitro*-1-*nitroso*-1-m-*tolyl*-cyclo*hexane* (1 g.), colourless needles (from pyridine–light petroleum), m. p. 195—197° (Found : C, 63·2; H, 6·3; N, 11·4%).

The former afforded, as above, the amine (10 g. from 20 g.), b. p. 125°/3 mm. [*benzoyl derivative*, needles (from ether), m. p. 120—123° (Found : C, 82·3; H, 8·1; N, 5·1%)], and a neutral *substance*, m. p. 124—125° (from methanol) (Found : C, 77·3; H, 8·5; N, 6·9. $C_{13}H_{17}ON$ requires C, 76·9; H, 8·4; N, 6·9%), and finally 1 : 2 : 3 : 4 : 4a : 10a-*hexahydro-6*(*or* 8)-*methyl-9-phenylphenanthridine hydrochloride*, m. p. 226—227° (from acetone–ether) (Found : C, 76·9; H, 6·6%).

Addition of Dinitrogen Trioxide to 1-p-*Tolyl*cyclo*hexene*.—Treatment of the *cyclo*hexene [8] (40 g.) according to procedure (*a*) gave 1-*nitro*-2-p-*tolyl*cyclo*hexene* (20 g.), b. p. 139°/0·1 mm. (Found : C, 72·0; H, 6·8%), and 2-*nitro*-1-*nitroso*-1-p-*tolyl*cyclo*hexane* (4 g.), yellow needles (from methanol), m. p. 228° (decomp.) (Found : C, 62·8; H, 6·4; N, 11·2%).

The former gave, as above, *cis*-2-*p*-tolyl*cyclo*hexylamine, b. p. 97°/0·4 mm. [*benzoyl derivative*, needles (from ether), m. p. 136—137° (Found : C, 81·5; H, 7·6; N, 5·2%)], a neutral *substance*, needles (from alcohol), m. p. 173° (Found : C, 76·6; H, 8·6; N, 7·0%), and 1 : 2 : 3 : 4 : 4a : 10a-*hexahydro-7-methyl-9-phenylphenanthridine hydrochloride* (from alcohol–ether), m. p. 209° (Found : C, 76·8; H, 7·2%).

Addition of Dinitrogen Trioxide to 1-*Phenyl*cyclo*pentene*.—Treatment of the *cyclo*pentene [9] (19 g.) according to procedure (*a*) gave 1-*nitro*-2-*phenyl*cyclo*pentene* (9 g.), b. p. 105—108°/0·2 mm. (Found : C, 69·6; H, 5·7. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8%).

This afforded 2-phenyl*cyclo*pentylamine, b. p. 80—82°/0·7 mm. [*benzoyl derivative* (from ether), needles, m. p. 154° (Found : C, 82·0; H, 7·5; N, 5·3. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%)], and 3 : 4-*dihydro*-1-*phenyl*cyclo*penta*[c]*isoquinoline hydrochloride* (0·3 g. from 3 g.) (from alcohol–ether), m. p. 214° (Found : C, 71·7; H, 6·9. $C_{18}H_{18}NCl,H_2O$ requires C, 71·6; H, 6·6%).

Addition of Dinitrogen Trioxide to 1-*Phenyl*cyclo*heptene*.—Treatment of 1-phenyl*cyclo*-heptene [10] (5 g.) according to procedure (*a*) gave 1-*nitro*-2-*phenyl*cyclo*heptene* (3 g.), b. p. 128°/2 mm. (Found : C, 72·0; H, 7·1. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9%).

We thank the Government of India and The East India Pharmaceuticals Works Ltd., Calcutta, for the award of scholarships (to K. N. and N. A. respectively), and Mr. S. Selvavinayagam for microanalyses.

PRESIDENCY COLLEGE, MADRAS. [*Received, November 22nd*, 1955.]

[8] Sabatier and Mailhe, *Compt. rend.*, 1904, **138**, 1323.
[9] Denisenko, *Ber.*, 1936, **69**, 1353.
[10] Pines, Edeleanu, and Ipatieff, *J. Amer. Chem. Soc.*, 1945, **67**, 2193.

824. *Studies in Aromatic Nucleophilic Replacement. Part VI.* Some Effects of Alkyl Groups.*

By C. W. L. Bevan, T. O. Fayiga, and J. Hirst.

The influence of *ortho-*, *meta-*, and *para*-methyl and *-tert.*-butyl groups on the rate of replacement by methoxide ion of the fluorine of *m*-fluoronitrobenzene has been studied. The fluorine was activated by a *meta*-nitro-group to limit steric effects at the reaction centre to those attributable to an alkyl group. Reaction rates and Arrhenius parameters are recorded. The results are discussed in terms of the polar and steric effects of alkyl groups and the marked steric effect of an *ortho-tert.*-butyl group is noted. The preparation and characterisation of certain new alkylfluoronitrobenzenes are recorded.

The polar and steric effects of alkyl groups have been extensively studied.[1] The effects of alkyl groups on halogenation in *ortho-* and *para*-positions have been investigated by de la Mare and Robertson [2] and by Berliner and Berliner,[3] and the activating effects of methyl and *tert.*-butyl groups on all three positions in nitration have been discussed by Cohn, Hughes, Jones, and Peeling.[4] Recently, Berliner, Berliner, and Nedilow,[5] have evaluated the relative effects towards iodination of alkyl groups in the *meta*-position. The deactivating influence of *para*-alkyl groups on aromatic nucleophilic replacement has been noted by Bevan, Hughes, and Ingold [6] and by Berliner and Monack; [7] recently, analogous effects of *ortho-* and *para*-methyl groups have been recorded by Bolto, Miller, and Williams.[8]

A series of alkyl-substituted *m*-fluoronitrobenzenes † have been prepared, and their rates of reaction with methoxide ion in absolute methanol measured. The objects were to obtain information as to the effect of *ortho-*, *meta-*, and *para*-substitution by alkyl groups on the rate of nucleophilic replacement of an activated fluorine atom, to compare the effects of methyl and *tert.*-butyl groups in the *meta*-position, and possibly to obtain information as to the mode of transmission of the inductive effect through the benzene ring. The fluorine atom removed as fluoride ion was activated by a *meta*-nitro-group in order

Table 1. *k_2 (in l. sec.$^{-1}$ mole^{-1}) for reaction of alkyl-substituted* 3-*fluoro*-1-*nitrobenzenes with methoxyl ion in absolute methanol.*

Unsubstituted [9]		4-Methyl		5-Methyl		6-Methyl	
T	10^5k_2	T	10^5k_2	T	10^5k_2	T	10^5k_2
97·87°	5·73	100·0°	0·798	100·00°	3·05	109·95°	1·92
112·45	25·0	109·95	2·15	109·95	8·26	120·1	5·05
119·92	51·3	120·1	5·64	120·1	20·6	130·4	12·7
129·4	123	130·4	13·3	130·4	53·9		

4-*tert.*-Butyl		5-*tert.*-Butyl		6-*tert.*-Butyl	
T	10^5k_2	T	10^5k_2	T	10^5k_2
130·2°	2·63	99·80°	2·12	100·0°	0·690
		110·2	5·84	109·6	1·84
		130·2	39·9	120·1	5·28
				130·4	14·3

* Part V, *J.*, 1956, 469.

† For convenience of discussion all substituted nitrobenzenes are numbered from $NO_2 = 1$ in this section.

[1] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953.

[2] Robertson, de la Mare, and Swedlund, *J.*, 1943, 279; *J.*, 1953, 782, and other papers in this series.

[3] Berliner and Berliner, *J. Amer. Chem. Soc.*, 1949, **71**, 1195.

[4] Cohn, Hughes, Jones, and Peeling, *Nature*, 1952, **169**, 291.

[5] Berliner, Berliner, and Nedilow, *J. Amer. Chem. Soc.*, 1954, **76**, 507; Berliner and Berliner, *ibid.*, p. 6179.

[6] Bevan, Hughes, and Ingold, *Nature*, 1953, **171**, 301.

[7] Berliner and Monack, *J. Amer. Chem. Soc.*, 1952, **74**, 1574.

[8] Bolto, Miller, and Williams, *J.*, 1955, 2929.

[9] Bevan and Bye, *J.*, 1954, 3091.

to eliminate from the reaction centre steric effects other than those due to alkyl groups. Rate constants and Arrhenius parameters are summarised in Tables 1 and 2.

TABLE 2. *Comparison of* 10^6k_2 *(in l. sec.*$^{-1}$ *mole*$^{-1}$*) at* 130·4° *and Arrhenius parameters* ($k_2 = Be^{-E/RT}$) *for alkyl-substituted* 3-*fluoro*-1-*nitrobenzenes with methoxyl ion in absolute methanol.*

	Unsub.	4-Me	5-Me	6-Me	4-Bu	5-Bu	6-Bu
10^6k_2	1350	133	539	127	26	407	143
$\log_{10}B$	12·8	11·2	12·1	11·5	—	12·1	12·3
E (kcal.)	28·9	27·8	28·3	28·4	—	28·6	29·8

Discussion.—Relative rate constants for the 5-alkyl-3-fluoro-1-nitrobenzenes show that deactivation of this type of nucleophilic displacement follows the order $Bu^t > Me > H$. This corresponds with the electron-release effects found by Hughes *et al.*[4] in the *para*-nitration of alkylbenzenes and by Berliner *et al.*[5] in the *meta*-iodination of *p*-alkylphenols and -anilines. It is noteworthy that the ratio of rates of *meta*-nitration—found by the former authors—though in the reverse direction corresponds rather closely with those noted here :

$$k(m\text{-Me})/k(m\text{-Bu}^t) = 0{\cdot}63 \text{ for nitration}$$

$$k(m\text{-Bu}^t)/k(m\text{-Me}) = 0{\cdot}74 \text{ for nucleophilic replacement of fluorine}$$

At all temperatures at which comparative rate constants were measured it is seen that deactivation by 6- and 4-methyl substituents is about equal and about four times greater than that effected by 5-methyl groups. This corresponds with a more effective transfer of charge from the *ortho*- and the *para*-position by resonance or with the operation of hyperconjugation or both. The fact that deactivation from the *meta*-position is more effective in the case of a *tert.*-butyl group, whereas here and in previous cases investigated [6,7] the methyl group is most effective from the *para*-position, indicates that hyperconjugation is certainly operative.

Unfortunately, examination of the *tert.*-butyl case, in which C–H hyperconjugation would not arise, is complicated by the possibility of steric interaction between the 6-*tert.*-butyl group and the activating nitro-group which would lead to a decrease in the activating influence of the latter by its being forced out of coplanarity with the benzene ring. The activation energy for the present case, *viz.*, ~30 kcal., is significantly greater than for others and for the unsubstituted compound which are all 28—29 kcal. Deactivation due to steric inhibition of resonance would of course be superposed on retardation owing to electron release to the reaction site. The ratio of the effects, *p-tert.*-butyl : *p*-methyl, has been determined in aromatic nucleophilic displacement by Bevan, Hughes, and Ingold [6] as 1·76 and by Berliner and Monack [7] as 1·17. The former found that in no circumstance in a bimolecular nucleophilic displacement does the effect on the rate constant of a *para*-methyl group exceed twice that of a *tert.*-butyl group and even in the strongly electron-demanding unimolecular solvolysis of diphenylmethyl chloride in aqueous acetone [10] the ratio of rate constants is 2·32. We may therefore safely take this figure as an upper limit in the present case. If it is assumed that the rate for the 6-methyl compound is unaffected by steric inhibition of resonance, the value for the 6-*tert.*-butyl compound would, in the absence of this latter influence, be not more than

$$2{\cdot}32 \times 1{\cdot}27 \times 10^{-4} = 2{\cdot}92 \times 10^{-4} \text{ l. sec.}^{-1} \text{ mole}^{-1}$$

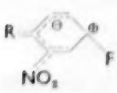
This value is considerably lower than that for the 5-*tert.*-butyl compound, showing that the polar influences of a *tert.*-butyl group are more effectively transferred from the *para*- than from the *meta*-position. This could be ascribed to C–C hyperconjugation.

In positions *para* to those at which occur aromatic nucleophilic displacements, which are inhibited by electron release, methyl groups have a greater retarding effect than *tert.*-butyl groups,[6,7] whereas in the *para*-nitration of alkylbenzenes,[4] which is accelerated by electron release, the *tert.*-butyl group has a greater facilitating influence than the methyl group. This apparent contradiction can be considered on the following basis.

[10] Hughes, Ingold, and Taher, *J.*, 1940, 949.

In aromatic nitration the nitronium ion which is a powerful electrophile can attach itself to the π-electron system of the reactive carbon atom during the process of rehybridisation to the sp^3-like bonds of the transition state at a much earlier stage than, say, a methoxide ion can form a partial bond with the nucleus of a reactive aromatic carbon atom. Thus it is reasonable to suppose that the creation of the former transition state is largely influenced by the permanent polarisation effects, both inductive and hyperconjugative, which are set up by alkyl groups. Evidence from the dipole moments of alkylbenzenes and from the effects of *meta*-alkyl groups in both electrophilic and nucleophilic displacements indicates a permanent electron release in the order *tert.*-butyl > methyl > hydrogen.

It is generally agreed that the transition state of activated aromatic nucleophilic displacements takes place *via* a transition state (or transition states if an intermediate is postulated) in which benzenoid resonance is lost and the reactive carbon atom has a tetrahedral disposition of valencies. Thus in a reaction such as the one considered here, the transition state of the replacement cannot be formed until the molecule being attacked has to a considerable extent been polarised to the form shown inset. It has been clearly established that the order of mesomeric effects of alkyl groups is methyl > *tert.*-butyl > hydrogen.[10a] Thus the development of a positive charge at the reactive carbon atom will involve a greater loss of resonance energy in the case of *ortho*- and *para*-methyl groups than occurs with corresponding *tert.*-butyl groups, so that in the absence of steric effects alkyl groups should inhibit activated aromatic nucleophilic replacements in the order methyl > *tert.*-butyl > hydrogen. This is in fact the order always found.[6,7]



(R = alkyl group)

Finally, the marked deactivating influence of an *ortho-tert.*-butyl group shown by the rate constants in Table 2 confirms the interpretation by Hughes *et al.*[4] of the influence of this group on nitration as being largely steric in origin.

Experimental

Materials.—All solids used in the kinetic measurements were recrystallised to constant m. p. from the appropriate solvent; liquids were purified by repeated distillation at reduced pressure.

1-*Fluoro*-2-*methyl*-5-*nitrobenzene.*—Commercial 2-methyl-5-nitroaniline was acetylated, and the acetyl compound crystallised to constant m. p., hydrolysed with 70% sulphuric acid, and reconverted into the amine with ammonia. The recrystallised amine was converted by Stech and Fletcher's modification[11] of the Schiemann reaction into the diazonium fluoroborate which decomposed to the required compound; b. p. 77°/4 mm., m. p. 35°.

1-*Fluoro*-4-*methyl*-3-*nitrobenzene.*—Prepared from commercial 4-methyl-5-nitroaniline by a method analogous to the above, this had b. p. 71°/3 mm., s. p. −8·8° to −8·9°.

1-*Fluoro*-3-*methyl*-5-*nitrobenzene.*—*p*-Toluidine was acetylated, nitrated, hydrolysed, and deaminated to 3 : 5-dinitrotoluene, which was reduced with potassium polysulphide to 3-amino-5-nitrotoluene. This was converted *via* the diazonium fluoroborate into the required *fluoro-compound*, m. p. 40·0—40·5° (from aqueous methanol) (Found: C, 54·4; H, 4·38; N, 9·0. $C_7H_6O_2NF$ requires C, 54·2; H, 3·9; N, 9·0%).

1-tert.-*Butyl*-2-*fluoro*-4-*nitrobenzene.*—*tert.*-Butylbenzene, prepared from benzene and *tert.*-butyl chloride, was nitrated. 2- and 4-*tert.*-Butylnitrobenzene were isolated by fractionation at 12 mm. and reduced to the corresponding amines. 2-*tert.*-Butylaniline (20 g.) was dissolved in concentrated sulphuric acid (200 g.) cooled to −10°, and the solution stirred vigorously while dry, finely powdered potassium nitrate (20 g.) was added gradually (1 hr.). The product was poured on a small quantity of ice at −10°, allowed to remain for 3 min., and the thick mass of nitro-amine sulphate was drained from excess of acid. The sulphate was basified with ammonia, and the base crystallised from aqueous alcohol; it had m. p. 71·5—72·5°. Some of these crystals were deaminated by using hypophosphorous acid, the nitro-compound reduced, and the acetyl derivative of the amine formed; m. p. 161—162°. Craig[12] gives for 4-*tert.*-butylacetanilide, m. p. 161—162°. Hence, by the above method nitration of 2-*tert.*-butylaniline

[10a] Baker and Hemming, *J.*, 1942, 191.
[11] Stech and Fletcher, *J. Amer. Chem. Soc.*, 1948, **70**, 439.
[12] Craig, *J. Amer. Chem. Soc.*, 1935, **57**, 195.

afforded the 5-nitro-derivative. The latter was converted *via* the diazonium fluoroborate into the desired *fluoro-compound*, b. p. 103·5—104°/3 mm., m. p. 12·5—13° (Found: C, 61·0; H, 6·5; N, 6·8. $C_{10}H_{12}O_2NF$ requires C, 60·9; H, 6·1; N, 7·0%).

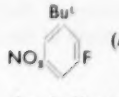
1-tert.-*Butyl*-4-*fluoro*-2-*nitrobenzene*.—4-*tert*.-Butyl-5-nitroaniline hydrochloride was prepared by Shoesmith and Mackie's method [13] and converted into the named *compound* in the usual way; it had b. p. 90—92°/7 mm. (Found: C, 61·0; H, 6·4; N, 6·6. $C_{10}H_{12}O_2NF$ requires C, 60·9; H, 6·1; N, 7·1%).

1-tert.-*Butyl*-3-*fluoro*-5-*nitrobenzene*.—*p*-Amino-*tert*.-butylbenzene was acetylated and nitrated; to avoid extensive decomposition of the product the following procedure was used. Finely powdered *p-tert*.-butylacetanilide (20 g.) was added during 15 min. to well-stirred fuming nitric acid (200 ml.) at 5°. The mixture was cooled to −10° and poured into much crushed ice and salt with vigorous stirring. The light yellow solid was collected on a spatula and placed in ice-cold ether over sodium hydrogen carbonate and ice, the mixture stirred and filtered, and the solid washed with dilute hydrochloric acid and much water, giving 4-acetamido-3 : 5-*tert*.-butyldinitrobenzene, m. p. 132—133° (yield 53%). This compound was deacetylated and then deaminated by Cohen and McCandlish's method,[14] giving 1-tert.-*butyl*-3 : 5-*dinitrobenzene*, m. p. 99·5—100·5° (Found: C, 53·4; H, 5·3; N, 12·8. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). This was reduced by the same authors' method to 3-tert.-*butyl*-5-*nitroaniline*, m. p. 73° (Found: C, 61·7; H, 7·2; N, 14·8. $C_{10}H_{14}O_2N_2$ requires C, 61·8; H, 7·3; N, 14·4%). Acetyl derivative, m. p. 159·5—160°. The amine was converted in the usual way *via* the diazonium fluoroborate into the required *fluoro-compound*, b. p. 76°/1 mm. (Found: C, 60·9; H, 6·2; N, 7·2. $C_{10}H_{12}O_2NF$ requires C, 60·9; H, 6·1; N, 7·1%).

Analysis of Products.—It is known [15] that *o*- and *p*-nitrotoluene and their derivatives develop deep colours on treatment with concentrated methanolic potassium hydroxide in the presence of air or other oxidising agent. The reactions under discussion were therefore carried out under an atmosphere of nitrogen and in most cases rate constants were determined over the range 10—20% of reaction; in this range the falling off in rate constants, attributable to side reactions, was negligible. The products of the reaction between methoxide ion and 1-fluoro-4-methyl-3-nitrobenzene, the case in which colour production was most pronounced, were analysed in order to confirm that the process being measured was the replacement of fluorine by methoxide ion.

Four portions, each 250 ml., of 0·03M-1-fluoro-4-methyl-3-nitrobenzene and 0·0507N-sodium methoxide in absolute methanol were heated under nitrogen in sealed ampoules for 13 days at 100·1°. The tubes were cooled, the contents made slightly acid with methanolic hydrogen chloride, and the methanol removed by slow distillation from a water-bath until the residual volume was 50 ml. The mixture of sodium fluoride and sodium chloride which crystallised during the evaporation was weighed, and the chloride estimated by Volhard's method. This, together with a correction for the solubility of sodium fluoride in methanol, showed that 0·004427 mole of sodium fluoride had been formed. Hence, if the replacement of fluorine by methoxide ion is the only reaction taking place, the amount of 4-methoxy-2-nitrotoluene formed would be 0·7401 g. The remaining methanol was distilled off, and diethyl phthalate (2 ml.) added as a chaser; the mixture was then fractionated through a good column at 22 ± 0·1 mm. The following fractions were obtained: (i) b. p. 105°/22 mm. (2 ml.), (ii) b. p. 105—148°/22 mm. (0·1 ml.), (iii) b. p. 148—150°/22 mm. (0·92 g.), (iv) b. p. 172°/22 mm. (chaser). Fraction (iii) had b. p. 265—267°/760 mm. (Found: OMe, 20·8. Calc. for $C_8H_9O_3N$: OMe, 18·6%). Knecht [16] gives for 4-methoxy-2-nitrotoluene, b. p. 266—267°. The only substance present that can give a methoxyl analysis other than the expected product is diethyl phthalate, and on this basis the product isolated contained 76·4% of 4-methoxy-2-nitrotoluene which corresponds to 95% of the fluoride ion liberated.

Evidently up to 30% of reaction, for practical purposes, the only reaction taking place is that with which this communication is concerned.



(A)

Kinetic Measurements.—Thermostat temperatures were steady to within ±0·05°. The reactions were carried out in sealed tubes under nitrogen, and their progress was followed as in previous papers in this series except that the indicator used was bromocresol-green–methyl-red.

[13] Shoesmith and Mackie, *J.*, 1928, 2334.
[14] Cohen and McCandlish, *J.*, 1905, **87**, 1257.
[15] Green and Baddiley, *J.*, 1908, **93**, 1721.
[16] Knecht, *Annalen*, 1882, **215**, 88.

Determination of k_2(l. sec.$^{-1}$ mole^{-1}) for reaction of 1-tert.-*butyl*-3-*fluoro*-5-*nitrobenzene* (*A*) *with methoxyl ion in absolute methanol.*

Initially, [Halide] = 0·0300M, [OMe$^-$] = 0·06678M. Temp. 130·2°. Concns. in ml. of 0·0213N-NaOH solution per 9·01-ml. sample.

t (hr.) ...	0	3	3·5	4·0	4·5	5·1	5·5	6·5	7·5	9	10	11	12	12·5
[NaOH]	27·65	25·12	24·82	24·50	24·10	23·75	23·56	23·03	22·60	21·74	21·40	21·13	20·79	20·59
[Halide]	12·11	9·58	9·28	8·96	8·56	8·21	8·01	7·49	7·06	6·20	5·86	5·59	5·25	5·05
10^4k_2 ...	—	3·48	3·41	3·41	3·52	3·50	3·48	3·46	3·41	3·60	3·55	3·46	3·47	3·51

Mean $k_2 = 3·48 \times 10^{-4}$. Duplicate = $3·42 \times 10^{-4}$.

Corrected for solvent expansion, $k_2 = 3·99 \times 10^{-4}$.

One of us (T. O. F.) thanks the Council of University College, Ibadan, for a scholarship during the tenure of which this work was carried out.

UNIVERSITY COLLEGE, IBADAN, NIGERIA. [*Received, March 13th*, 1956.]

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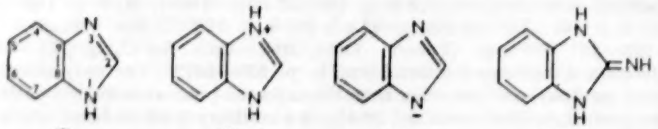
825. *A Theoretical Investigation of the Chemical Reactivity of Benziminazole.*

By R. D. BROWN and M. L. HEFFERNAN.

A theoretical investigation of the benziminazole molecule by the molecular-orbital method indicates that electrophilic substitution in acidic media (*e.g.*, nitration) occurs in the free base and not in the benziminazolium cation; but in alkaline solution the substitution must occur in the benziminazole anion whenever it occurs preferentially in the 2-position. Other properties of benziminazoles are also interpreted in terms of the theoretical results. It is predicted that free radicals will attack the 4-position preferentially.

RECENTLY [1-5] we compared the results of calculations by the simple molecular-orbital approximation with the known chemical properties of some heterocyclic nitrogen compounds. In the present paper benziminazole is treated along the lines used for five-membered nitrogen heterocycles.[1,2] The approximations used for glyoxaline [1] have been adopted and in addition the overlap integral has been taken to be zero to simplify the calculations for the larger molecule. Theoretical results obtained for glyoxaline by neglecting overlap [2] do not differ qualitatively from those obtained with overlap included,[1] and the same is doubtless true for benziminazole.

π-Electron densities and atom-localization energies for electrophilic, nucleophilic, and homolytic substitutions have been calculated for various values of the electronegativity parameter, h, for the nitrogen atoms. Our earlier results suggest that from the viewpoint of the π-electrons the difference between the neutral benziminazole molecule (I), its cation



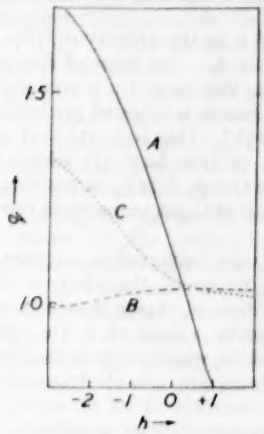
(I) (II) (III) (IV)

(II), and anion (III) can primarily be ascribed to a change in electronegativity of the nitrogen atoms. In particular they become *less* electronegative than carbon atoms in the anion (III).

The theoretical results are present in the Figures and Tables.

[1] Bassett and R. D. Brown, *J.*, 1954, 2701.
[2] Brown, *Austral. J. Chem.*, 1955, **8**, 100.
[3] Brown and Heffernan, *ibid.*, 1956, **9**, 83.
[4] Brown, *J.*, 1956, 272.
[5] Bassett, Brown, and Penfold, *Chem. and Ind.*, in the press.

FIG. 1. *π-Electron densities in benziminazole as a function of electronegativity of nitrogen.*



A, Position 2. *B*, Position 4. *C*, Position 5.

FIG. 2. *Electrophilic atom-localization energies.*

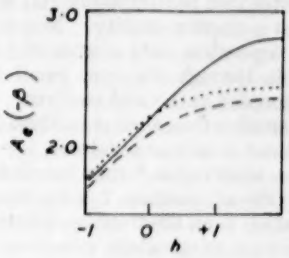


FIG. 3. *Nucleophilic atom-localization energies.*

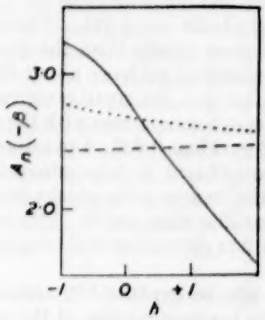


FIG. 4. *Radical atom-localization energies.*

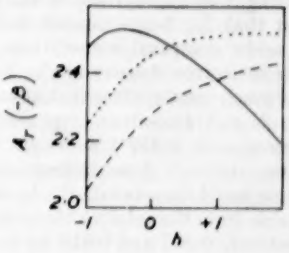


TABLE 1. *π-Electron densities.*

Position	h:	−∞	−3	−2	−1	−0·5	0	+0·5	+1	+2	+∞
1		0·00	0·27	0·48	0·86	1·07	1·25	1·40	1·52	—	2·00
2		2·00	1·73	1·60	1·39	1·26	1·11	0·96	0·81	—	0·00
4		1·33	0·99	1·00	1·02	1·03	1·03	1·03	1·03	1·03	1·00
5		1·33	1·35	1·26	1·14	1·09	1·06	1·04	1·03	1·02	1·00
8		1·33	1·53	1·46	1·28	1·18	1·10	1·04	1·01	—	1·00

TABLE 2. *Electrophilic atom-localization energies (units of −β).*

Position	h:	−1	−0·5	0	+0·5	+1	+2
2		1·73	1·96	2·22	2·46	2·65	2·80
4		1·66	—	2·12	2·23	2·30	2·37
5		1·67	—	2·23	2·35	2·41	2·46

TABLE 3. *Nucleophilic atom-localization energies (units of −β).*

Position	h:	−1	−0·5	0	+0·5	+1	+2
2		3·22	3·10	2·81	2·46	2·12	1·59
4		2·42	—	2·44	2·46	2·47	2·49
5		2·78	—	2·68	2·65	2·62	2·58

TABLE 4. *Homolytic atom-localization energies (units of −β).*

Position	h:	−1	−0·5	0	+0·5	+1	+2
2		2·48	2·53	2·51	2·46	2·39	2·19
4		2·04	—	2·28	2·34	2·38	2·43
5		2·23	—	2·46	2·50	2·51	2·52

Electron Densities.—The π-electron densities at the three different carbon atoms are plotted against the electronegativity parameter in Fig. 1. They suggest an interpretation of the substitution of benziminazole as follows:

For the neutral molecule the appropriate value [4] of h is in the vicinity of 0·5. In this region the most highly charged carbon atom is at position 5. The value of h applying to the protonated benziminazole (II) is probably 1—2 and in this range the 4-position has the greatest π-electron density. Now in acid media benziminazole is nitrated predominantly [6] in the 5-position, only a trace of 4-isomer being obtained.[7] This suggests that nitration proceeds through the very small equilibrium amount of free base (I) which remains unprotonated in the acid medium. For the free base the charge density at position 4 is not much smaller than that at position 5, so that the isolation of slight amounts of the 4-nitro-compound is understandable.

The observation [8] that benziminazole is quantitatively iodinated in aqueous sodium hydroxide at position 2 may also be interpreted in terms of the electron densities. Iodination is an electrophilic substitution [9] and the position of attack would be expected to be that of greatest π-electron density. For negative values of h the charge at position 2 is far greater than that on any other carbon atom, which suggests that benziminazole is attacked in a form in which the nitrogen atoms are less electronegative than carbon atoms. It has been suggested [1,2,5] that this situation exists in anions such as (III), and quantum-mechanical calculations of electronegativities for negatively charged, conjugated nitrogen atoms confirm this reversal.[10] Further, if the iodination of benziminazole proceeds through the anion it will be analogous to that of glyoxaline.[11]

The π-electron densities of the 2-positions in glyoxaline and benziminazole for $h = -1$, which might be appropriate for the anions, are respectively 1·458 and 1·391. These values suggest that the benziminazole anion will be iodinated more slowly than the glyoxaline anion under comparable conditions, but there is no experimental evidence about this.

The π-electron density at the 2-position in the free base (*i.e.*, for small positive values of h) is much smaller than that at any other position. From a comparison with the charges at the 2- and 4-position of pyridine [3] (for $h = 0·5$: 2-pyridine 0·923, 4-pyridine 0·950, 2-benziminazole 0·959*) we might expect a 2-methyl substituent in benziminazole to be reactive. Indeed, 2-methylbenziminazole, like α-picoline, reacts with aldehydes [12] and other carbonyl compounds.[13] In contrast, 2-methylglyoxaline does not.[14] This is understandable from the relative electron densities at position 2 in glyoxaline and benziminazole (respectively 0·907 and 0·810 for $h = 1$).

The stability of benziminazolecarboxylic acids may also be explained in terms of the calculated electron distribution. Carboxyl groups in the benzene portion of the molecule are very stable to heat, whereas benziminazole-2-carboxylic acids are very readily decarboxylated.[15] Decarboxylation by the unimolecular mechanism [16] is facilitated by a low electron density at the carbon atom carrying the carboxyl group. However, when the electron density on that atom is neither high nor low, decarboxylation by either the S_E1 or the S_E2 mechanism proceeds with difficulty.

The properties of the aminobenziminazoles also reflect the general features of the

* The value of h appropriate for the benziminazole molecule is probably larger than that for pyridine,[3] so that the comparable charge for position 2 of benziminazole is probably appreciably smaller than this value. The observed orientation of nitration and the reactivity of the 2-methylbenziminazole relative to α-picoline suggest that the appropriate value of h is about 0·6.

[4] Fischer and Hess, *Ber.*, 1903, **36**, 3967.
[5] Fries, *Annalen*, 1927, **454**, 121.
[6] Pauly and Gundermann, *Ber.*, 1908, **41**, 3999.
[7] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953, p. 291.
[8] Brown and Penfold, *J. Chem. Phys.*, 1956, **24**, 1259.
[9] Ridd, *J.*, 1955, 1238.
[10] Bamberger and Berle, *Annalen*, 1893, **273**, 303.
[11] van Alphen, *Rec. Trav. chim.*, 1940, **59**, 289.
[12] Hofmann, "Imidazole and Its Derivatives. Part I." Interscience Publ. Inc., New York, 1953, p. 278.
[13] *Op. cit.*, p. **314**.
[14] B. R. Brown, *Quart. Rev.*, 1951, **5**, 131.

π-electron distribution. *Bz*-Aminobenziminazoles are typical aromatic amines,[17] in agreement with the fact that the charge densities in the benzene ring lie very close to unity in the uncharged benziminazole molecule. In contrast a 2-amino-group is not basic, which indicates a low π-electron density at the 2-position: its tendency to exist in the imide form (cf. IV) and general similarity to the amino-group in 2- and 4-aminopyridine is to be associated with a low π-electron density at the position carrying it.

The calculated electron distribution in uncharged benziminazole also explains why the 2-halogen substituents are readily displaced under conditions which leave *Bz*-substituents unchanged,[18] in agreement with the very much lower charge density at the 2-position.

Atom-localization Energies.—The electrophilic localization energies are shown as functions of h in Fig. 2. For positive values of h such as would be appropriate for the free base and the cation (II), the localization energy is smallest for position 4, and it is not possible to obtain the smallest localization energy at position 5 for any choice of h. The substitutions in the free base are thus orientated in accordance with the electron densities rather than the localization energies, *i.e.*, the chemical " non-crossing rule " does not apply.[19]

For values of h less than -1 the localization energy is still smaller at other positions than at position 2. Thus the " non-crossing rule " breaks down also for the anion (III), since it is hardly likely that the appropriate value of h for this entity will be much less than -1.

It is interesting that a somewhat similar breakdown of the non-crossing rule was found for glyoxaline,[1,2] and here also the orientation was in agreement with the charge densities rather than with the localization energies.

The nucleophilic localization energies, shown in Fig. 3, do, however, agree with the π-electron distribution. For h greater than 0·5, position 2 has the smallest localization energy; for more negative h, the localization energy is smallest for position 4.

The radical localization energies are plotted in Fig. 4. The results enable us to predict that in the free base radical attack will occur preferentially at position 4. The use of free valencies as alternative criteria of reactivities towards radical substitution cannot be justified for benziminazole;[20] however, it is of interest that for $h = 0{\cdot}5$ the free valencies of positions 2, 4, and 5 are respectively 0·416, 0·447, and 0·405, in agreement with the radical-localization energies. There appear to be no experimental data, *e.g.*, on phenylation or vapour-phase bromination, which might indicate the position of attack of benziminazole by radicals.

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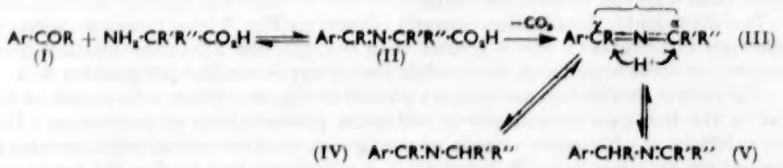
[17] Lindemann and Krause, *J. prakt. Chem.*, 1927, **115**, 256.
[18] *Op. cit.*, p. 302.
[19] R. D. Brown, *Quart. Rev.*, 1952, **6**, 63.
[20] R. D. Brown, *J. Chim. phys.*, 1953, **50**, 109.

826. *Triad Prototropic Systems. Part IV.* The Effect of Substituents on the Mobility of the Azomethinecarboxylic Acids derived from Ketones.*

By F. G. Baddar and Sayed A. M. Sherif.

The degradation of α-amino-acids by ketones such as fluorenones, benzophenones, and acetophenones is governed by temperature and by the polar character of the substituents present in the ketone, and of those attached to the α-carbon atom of the amino-acid. Thus, the percentage of degradation increases when an electron-attracting group (*e.g.*, NO_2) is attached at the *para*-position to the carbonyl group of the ketone, or by rise of temperature. The increase by these two factors appears to be due to a similar increase in the percentage of decarboxylation of the intermediate azomethinecarboxylic acids. Substituted benzophenones and acetophenones are less effective than the corresponding aldehydes.

This investigation is a continuation of the study of the effect of decarboxylation, and of substituents, on the mobility of the azomethinecarboxylic acids derived from the condensation of ketones such as fluorenones, benzophenones, and acetophenones with α-amino-acids. It supports the previous assumption by Baddar and Iskander,[1] that the reaction



between α-amino-acids and carbonyl compounds is reversible,[2] since the amount of degradation of alanine with fluorenone increased on increase in the molecular proportion of fluorenone (cf. Table 1). It reached its maximum value (63%) when 1 mol. of alanine was heated with 1 mol. of fluorenone for 30 hr., or with 4 mols. for 3 hr. The results also support the same authors' conclusion that the decarboxylation of the intermediate acid (II) to the mesomeric anion (III) is favoured by rise of temperature,[3] and increase in the electron-attracting power [4] of the groups Ar, R, and R′ (cf. Table 5).

The fact that the percentage of decarboxylation of phenylglycine with 4 : 4′-dinitrobenzophenone and 4-nitroacetophenone was found to be the same, in spite of the fact that R in the former ketone is an electron-attracting and in the latter is an electron-repelling group, may be attributed to steric factors, which inhibit the formation of the azomethinecarboxylic acid in the former case.

The relative rates at which a proton is taken up at the two positions in the mesomeric anion (III) to give isomers (IV) and (V) depends on (1) the electron density at the α- and γ-carbon atoms, and (2) the relative stabilities of the resulting Schiff's bases. These two factors may operate together, favouring the formation of one of the isomers (*e.g.*, when Ar = R = *p*-NO_2·C_6H_4, and R′ = Ph), or may oppose each other, favouring the formation of a different isomer (*e.g.*, when Ar = R = *p*-NO_2·C_6H_4, and R′ = Me).

The greater percentage of degradation of phenylglycine with 4-nitroacetophenone than with 4 : 4′-dinitrobenzophenone (Table 3A), although both decarboxylated it to the same extent (Table 5), may be attributed to the lower stability of isomer (IV; R = Me) than of isomer (IV; R = *p*-NO_2·C_6H_4).

* Part III, *J.*, 1954, 209.

[1] Baddar and Iskander, *J.*, 1954, 203.
[2] Cf. Gulland and Mead, *J.*, 1935, 210.
[3] Brown, *Quart. Reviews*, 1951, **5**, 131.
[4] Cf. McIntire, *J. Amer. Chem. Soc.*, 1947, **69**, 1377.

p-Methoxyphenylglycine was found to be more easily degraded with strong degrading agents, and less so with weak degrading agents, than phenylglycine (cf. Table 3). This may be due to the fact that, with the former agents, decarboxylation is nearly complete (cf. Table 5), and thus, the percentage of degradation will be directly proportional to the electron density at the γ-carbon atom in the anion (III). With weak degrading agents the rate of decarboxylation will be a controlling factor.

The previous assumption by Baddar and Iskander [1] that the increase in the percentage of degradation, on rise of temperature, is mainly due to a corresponding increase in the percentage of decarboxylation is supported by the following fact: the percentage increase in degradation of phenylglycine with 4 : 4′-dinitrobenzophenone, caused by rise of temperature from 100° to 115—120° (cf. Table 3A), was nearly the same as the percentage increase in decarboxylation (cf. Table 5).

The increase in the degrading power of the ketones studied in the present investigation by the introduction of nitro-groups cannot be due to an oxidising action of the nitro-group, since tetranitrodiphenylmethane failed to degrade alanine.

In general, benzaldehydes are stronger degrading agents than the corresponding benzophenones and acetophenones (cf. the present results with those in Parts I [6] and II [1]). Similarly, the percentage of decarboxylation of phenylglycine by benzaldehydes was higher than that by benzophenones (cf. Table 5). This may be mainly due to a greater tendency of amino-acids to condense with aldehydes than with ketones.

Experimental

Degradation of Alanine.—A mixture of alanine (0·089 g., 0·001 mole) and the required ketone (0·001 mole) in 75% (v/v) aqueous pyridine or in dry pyridine (10 ml.) was heated in an oil-bath at 115—120°, or on a boiling-water bath, under carbon dioxide for 3 hr. (cf. Baddar and Iskander [1]). The liberated acetaldehyde was estimated as its 2 : 4-dinitrophenylhydrazone. The efficiency of the apparatus was determined by a method similar to that mentioned in Part II; [1] in two experiments recovery of acetaldehyde from paraldehyde was 93·36 and 93·65%.

The results, although not of absolute quantitative significance, are reproducible within ±5%. The results (each the mean of at least two runs) are in Table 1.

Table 1.

	Degradation (%) in		
Degrading ketone	75% C_5H_5N (115—120°)	C_5H_5N (115—120°)	75% C_5H_5N (water-bath)
2 : 3 : 6 : 7-Tetranitrofluorenone	18·6	—	14·9
2 : 4 : 7-Trinitrofluorenone	16·3	—	10·7
Fluorenone	15·8 [a]	—	8·9 [b]
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	4·2	—	1·8
4 : 4′-Dinitrobenzophenone	3·1	—	1·4
3 : 3′-Dinitrobenzophenone	0	—	—
4-Nitrobenzophenone	0	1·4	—
4 : 4′-Dichlorobenzophenone	0	—	—
Benzophenone	0	—	—
4-Nitroacetophenone	Trace	16·4	—
3-Nitroacetophenone	0	13·2	—
4-Chloroacetophenone	0	2·5	—
2-Chloroacetophenone	0	2·5	—
2 : 4 : 2′ : 4′-Tetranitrodiphenylmethane	0	—	—

[a] Three experiments were carried out, the proportions (in moles) of alanine and fluorenone respectively being: (*a*) 0·001, 0·002; (*b*) 0·002, 0·001; (*c*) 0·001, 0·004. The percentages of degradation were 43·4, 42·5, and 63·5, respectively. [b] This experiment was repeated and the heating was continued until no more acetaldehyde was liberated (63·2% after 30 hr.).

Degradation of α-Aminoisobutyric Acid.—A mixture of this acid (0·21 g., 1 mol.) and the degrading ketone (1 mol.) in 75% (v/v) pyridine (10 ml.) was treated as with alanine. The liberated acetone was collected as its 2 : 4-dinitrophenylhydrazone. In a control experiment, a known weight of pure "AnalaR" acetone was treated identically. In four experiments the

[5] Baddar, *J.*, 1949, s 163.
[6] *Idem*, *J.*, 1950, 136.

recovery of acetone was 66·6, 64·3, 65·7, and 65·1%. The mean (65·4%) was used in the calculation of the values in Table 2A, which were reproducible within ±5% (based on the weight of the 2 : 4-dinitrophenylhydrazone). It appeared that the low recovery was due to the solubility of acetone 2 : 4-dinitrophenylhydrazone in 2N-hydrochloric acid.

Degradation of 1-*Aminocyclohexanecarboxylic Acid.*—The α-amino-acid [1] (0·14 g., 1 mol.) was heated with the requisite ketone as in the preceding experiment. The reaction mixture was acidified with 2N-hydrochloric acid (100 ml.) and distilled in a stream of carbon dioxide. The *cyclo*hexanone was determined by a similar procedure to that used by Baddar and Iskander.[1] Recovery of *cyclo*hexanone in two experiments was 91·56 and 92·1 (mean 91·8%). The results are in Table 2B.

TABLE 2.

	Degradation (%) in 75% C_5H_5N			
	A		B	
Degrading ketone	(115—120°)	(water-bath)	(115—120°)	(water-bath)
Isatin	57·6 [a]	40·8	—	—
2 : 3 : 6 : 7-Tetranitrofluorenone	18·5	1·9	20·6	13·5
2 : 4 : 7-Trinitrofluorenone	0	—	6·0	0·8
Fluorenone [c]	0	—	0 [c]	—
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	2·7	1·4	10·0	4·2
4 : 4′-Dinitrobenzophenone	0	—	*ca.* 0·4	—
3 : 3′-Dinitrobenzophenone	—	—	0	—
4-Nitrobenzophenone	—	—	0	—
4 : 4′-Dichlorobenzophenone	—	—	0	—
4-Nitroacetophenone [c]	0 [b]	—	0	—

[a] Cf. Baddar and Iskander.[1] [b] When the experiment was carried out in dry pyridine no degradation took place. [c] These ketones could be distilled in steam, and the distillate gave a 2 : 4-dinitrophenylhydrazone, which proved to be that of the original ketone.

Degradation of Phenylglycine.—Phenylglycine (0·15 g., 1 mol.) was heated with the degrading ketone (1 mol.) in 75% pyridine (10 ml.) in the usual manner. For the estimation of benzaldehyde produced (Table 3A), the following procedures were adopted.

(i) For ketones which were not volatile in steam, such as nitrofluorenones and benzophenones, and for nitro-ketones which were volatile in steam, procedures (i) and (ii), respectively, adopted by Baddar and Iskander [1] were used. Control experiments with benzaldehyde gave 82·0% and 92·1% recovery, respectively.

(ii) For fluorenone, the mixture was distilled with 2N-hydrochloric acid (200 ml.) until 10—15 ml. remained in the flask. The distillate was extracted with ether (80 ml.), then treated with saturated aqueous sodium hydrogen sulphite (20 ml.). The sulphite layer was warmed with excess of 2 : 4-dinitrophenylhydrazine reagent, and the precipitated benzaldehyde hydrazone was dried and weighed. Control experiments with benzaldehyde gave 74·9% and 75·1% recovery.

TABLE 3.

	Degradation (%) in 75% C_5H_5N			
	A		B	
Degrading ketone	(115—120°)	(water-bath)	(115—120°)	(water-bath)
Isatin	—	—	100·0	98·3
2 : 3 : 6 : 7-Tetranitrofluorenone	54·9	20·7	23·0	11·2
2 : 4 : 7-Trinitrofluorenone	8·0	2·5	5·6	5·6
Fluorenone	15·6	13·6	8·6	4·5
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	27·8	4·2	9·7	4·7
4 : 4′-Dinitrobenzophenone	9·2	2·6	8·4	4·7
3 : 3′-Dinitrobenzophenone	0	—	0	—
4-Nitrobenzophenone	5·0	3·0	4·9	3·6
4 : 4′-Dichlorobenzophenone	0	—	0	—
3 : 3′-Dibromobenzophenone	0	—	0	—
4-Nitroacetophenone	26·0	13·2	14·6	5·6
3-Nitroacetophenone	3·8	2·4	3·5	2·8
p-Nitrodeoxybenzoin	0	—	—	—

Degradation of p-*Methoxyphenylglycine.*—*p*-Methoxyphenylglycine (0·18 g., 1 mol.) was heated with the carbonyl compound (1 mol.) in 75% pyridine as usual. For the estimation of *p*-anisaldehyde produced (Table 3B), the procedure was as for benzaldehyde except that 200 ml.

of 2N-hydrochloric acid were used instead of 100 ml. The α-amino-acid was found to be stable under the conditions of the experiments, and in absence of degrading agents.

The recoveries for (i) isatin, nitrofluorenones, and benzophenones, (ii) fluorenone, and (iii) nitroacetophenones were 97·1, 70·5, and 91·5%, respectively.

Degradation of m-*Nitrophenylglycine.*—*m*-Nitrophenylglycine (0·034 g.; 1 mol.) and the carbonyl compound (1 mol.) in 75% (v/v) aqueous pyridine (10 ml.) were heated in the usual manner.

(i) With ketones which were not volatile in steam, the reaction mixture was treated with 2N-hydrochloric acid (200 ml.), and distilled until no more *m*-nitrobenzaldehyde came over. It was estimated as its 2 : 4-dinitrophenylhydrazone. Control experiments showed that *m*-nitrophenylglycine was degraded in absence of the ketones to the extent of 5·8% and 5·1% at 115—120° and on a boiling-water bath, respectively. Control experiments with *m*-nitrobenzaldehyde gave 92·5% recovery.

With fluorenone the *m*-nitrobenzaldehyde was determined by an indirect method similar to that used in the case of chlorobenzaldehyde,[1] *i.e.*, reduction of *m*-nitrobenzaldehyde with stannous chloride before steam-distillation. Control experiments gave 78·4% recovery of fluorenone. Results are in Table 4.

TABLE 4.

Degrading ketone	Degradation (%) in 75% C_5H_5N (115—120°)	(water-bath)
Isatin	42·9	42·9
2 : 3 : 6 : 7-Tetranitrofluorenone	31·3	28·2
2 : 4 : 7-Trinitrofluorenone	42·9	42·4
Fluorenone	17·1	13·0
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	31·4	31·6
4 : 4′-Dinitrobenzophenone	35·8	35·7
3 : 3′-Dinitrobenzophenone	17·7	16·8
4-Nitrobenzophenone	30·9	29·4
4 : 4′-Dichlorobenzophenone	1·3	—
3 : 3′-Dibromobenzophenone	0	—

Decarboxylation of α-Amino-acids with Carbonyl Compounds.—The experiments were carried out in an apparatus composed of (i) a reaction flask attached to an inlet for pure nitrogen, and to a condenser ending with a trap of concentrated sulphuric acid, and (ii) absorption tubes containing soda-lime (similar to those used in quantitative analysis) attached to the trap.

Equimolecular amounts of the carbonyl compound and the amino-acid were placed in the reaction flask, and the air was swept out by a current of pure nitrogen (½ hr.). 75% Pyridine (10 ml.) was added, the absorption tubes were connected, and the reaction mixture was heated for 3 hr. on a boiling-water bath (unless otherwise stated), in a current of pure nitrogen. The reaction flask was then cooled in ice, and the current of nitrogen was passed for a further ½ hr. A control experiment to determine the efficiency of the apparatus was made by decomposing a known weight of " AnalaR " oxalic acid with potassium permanganate in presence of dilute sulphuric acid (recovery factor = 97·6%). The results are in Table 5.

TABLE 5.

Carbonyl compound	Decarboxylation (%) * 1	2	3	4	5	6
Isatin	—	81·5	92·6	—	—	95·5
2 : 3 : 6 : 7-Tetranitrofluorenone	—	2·3	34·9	—	—	16·3
Fluorenone	97·8	—	23·3	—	58·2 †	7·0
4 : 4′-Dinitrobenzophenone	—	—	23·3	69·9	—	—
3 : 3′-Dinitrobenzophenone	—	—	0	—	59·0	—
4-Nitroacetophenone	—	—	23·3	72·0	—	—
p-Nitrobenzaldehyde	—	—	100·0	—	—	—
2-Chloro-5-nitrobenzaldehyde	—	—	100·0	—	—	—
m-Nitrobenzaldehyde	—	—	22·0	58	—	—
o-Chlorobenzaldehyde	—	—	75·0	—	—	—
m-Chlorobenzaldehyde	—	—	58·0	—	—	—

* (1) Alanine heated for 30 hr. (2) α-Aminoisobutyric acid. (3) Phenylglycine. (4) Phenylglycine at 115—120° for 3 hr. (5) *m*-Nitrophenylglycine. (6) *p*-Methoxyphenylglycine.

† The same value was obtained in absence of fluorenone.

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827. *Fission of Esters of Carboxylic Acids by Boron Trichloride.*

By W. Gerrard and M. A. Wheelans.

With the exception of ethyl trichloroacetate, which did not undergo fission, all esters $R{\cdot}CO_2R'$ immediately formed a 1 : 1 complex with boron trichloride at −80°. Three modes of decomposition were discerned when the complex was heated. When R′ was primary, fission to acyl chloride and alkyl dichloroboronite occurred, accompanied by dissociation to the original compounds when R was $CHCl_2$ or Ph. When R′ was secondary or tertiary and R = Me, boron remained with the acyl part and fission occurred by formation of dichlorodiacetyl diborate and alkyl chloride, predominantly inverted with some loss in optical activity and usually accompanied by olefin, when R′ = Bu^s or 1-methylheptyl. Rearrangement to *tert.*-alkyl occurred when R′ = *neo*pentyl or 1 : 2 : 2-trimethylpropyl. Benzyl acetate gave a hydrocarbon polymer. Certain properties of the dichlorodiacetyl diborate are mentioned.

Extending the initial work [1] on the fission of esters by boron trichloride, we sought to discover the influence of the nature of R and R′ in $R{\cdot}CO_2R'$. In all the examples studied fission is preceded by formation of a complex, $R{\cdot}CO_2R',BCl_3$, and three modes of primary decomposition are discernible (1, 2, 3). For simple primary alkyl acetates, fission occurs

(1) $R{\cdot}CO_2R',BCl_3 \xrightarrow{\text{Dissocn.}} R{\cdot}CO_2R' + BCl_3$

(2) $R{\cdot}CO_2R',BCl_3 \xrightarrow{\text{Fission A}} R{\cdot}COCl + R'O{\cdot}BCl_2$

(3) $2R{\cdot}CO_2R',BCl_3 \xrightarrow[+\ R{\cdot}COR']{\text{Fission B}} R{\cdot}CO_2B(Cl){-}O{-}B(Cl){\cdot}O{\cdot}COR + 3R'Cl + R{\cdot}COCl$

(4) $RO{\cdot}BCl_2 \longrightarrow RCl + [BOCl \longrightarrow BCl_3 + B_2O_3]$

in accordance with (2), although the system is complicated by partial decomposition (4) of the alkyl dichloroboronite.[2] With *iso*butyl or *neo*pentyl esters, rearrangement led to formation of the tertiary alkyl halide, and when R = Pr or CMe_3, ethyl dichloroboronite was stabilised by the acyl chloride from which separation was difficult. A related phenomenon is the slow separation of acetyl chloride and boron trichloride. Benzyl acetate was peculiar in that the complex vigorously decomposed at 0°, presumably according to scheme (2), but gave a hydrocarbon polymer, a similar but not identical one being formed by the interaction of boron trichloride and benzyl alcohol. Because of the remarkable stability of *o*-nitrophenyl dichloroboronite,[3] the fission of the acetate to acetyl chloride and the dichloroboronite was readily demonstrated. With acetates, substitution of chlorine at the 2-carbon atom of R′ did not alter the primary mode of fission (2), but the dichloroboronite disproportionated [4] to the chloroboronate and trialkyl borate and boron trichloride (5).

(5) $2RO{\cdot}BCl_2 \longrightarrow (RO)_2BCl + BCl_3$; $3(RO)_2BCl \longrightarrow 2(RO)_3B + BCl_3$.

Substitution of chlorine at the 1-carbon atom of R in $R{\cdot}CO_2R'$ caused the complex to dissociate by mechanism (1) as well as to undergo fission by (2). Ethyl dichloroacetate was recovered in 75% yield, and ethyl trichloroacetate did not form a complex. Fission of ethyl benzoate by mechanism (2) was also accompanied by dissociation (1).

With secondary alkyl acetates boron remained almost entirely with the non-volatile part and the stoicheiometry appears to require 3 mols. of ester and 2 of boron trichloride. Analytical evidence points to the formation of a compound provisionally designated

[1] Frazer and Gerrard, *J.*, 1955, 2959.
[2] Gerrard and Lappert, *J.*, 1951, 1020, 2545; 1955, 3084.
[3] Colclough, Gerrard, and Lappert, *J.*, 1956, 3006.
[4] Edwards, Gerrard, and Lappert, *J.*, 1955, 1470.

" dichlorodiacetyl diborate " (reaction 3). Owing to its low solubility we have not been able to purify it; but on pyrolysis the specimens obtained in different experiments afforded acetyl chloride and boric oxide (reaction 6). With acetic acid (2 mols.) the compound gave hydrogen chloride and tetra-acetyl diborate [5] (reaction 7), and was formed by the interaction of acetic acid (3 mols.) with boron trichloride (2 mols.) as well as by interaction of the latter and acetic anhydride. The fate of R′ was in accordance with known properties

$$(6)\qquad (AcO{\cdot}BCl)_2O \xrightarrow{Heat} 2AcCl + B_2O_3$$

$$(7)\qquad (AcO{\cdot}BCl)_2O + 2AcOH \longrightarrow [(AcO)_2B]_2O + 2HCl$$

of the dichloroboronites of secondary alcohols in that olefin accompanies the alkyl chloride; the latter had predominantly inverted configuration and was mainly the tertiary alkyl chloride when R′ = $Me_3C{\cdot}CHMe$. There was insufficient evidence to show whether there was alkyl–oxygen fission, giving primarily the acyl dichloroboronite, which reacted further to afford the dichlorodiacetyl diborate, or whether the fission occurred as in (2), the different sequence of results being due to the known reactivity of a *sec.*-alkyl dichloroboronite, which might react with acetyl chloride in a way leading to formation of the dichlorodiacetyl diborate.

tert.-Butyl acetate behaved similarly to the *sec.*-butyl ester, and even afforded a precipitate of the diborate by addition of boron trichloride to the acetate in *n*-pentane at −10°.

Experimental

General Procedures.—Boron trichloride (1 mol.) was added dropwise to the ester (1 mol.) at −80°, whereupon the solid complex $R{\cdot}CO_2R',BCl_3$ was immediately formed, as shown by analysis of the solid precipitated from *n*-pentane and by the non-withdrawal of boron trichloride at low pressure. To effect ester fission the complex was heated at the required temperature, volatile matter being condensed at −80°, and the remainder was distilled. Isolation of the individual products of the primary and secondary reactions was difficult because of the following factors: only partial decomposition or disproportionation of the alkyl dichloroboronite, the stabilisation of the latter by acyl chloride, the loose complex formation between acyl chloride and boron trichloride, and in certain examples the appearance of the original ester owing to dissociation as distinct from decomposition of the complex. The acyl chloride and boron trichloride were separated by repeated distillations until the correct analysis (Cl, or Cl and B) was achieved; but the proportions of each constituent in the original mixture were determined by addition of pyridine to obtain the pyridine–acyl chloride compound which reacts with water, and the pyridine–boron trichloride compound which does not. By hydrolysis, proportions of constituents were assessed from the contents of chlorine and boron. The more volatile alkyl chlorides were separated from boron trichloride by fixing the latter as the pyridine complex and distilling the alkyl chloride.

In experiments with esters of secondary and tertiary alcohols, we were led to use different molecular ratios because of the different type of result obtained, and attention was centred on the isolation of dichlorodiacetyl diborate which could not be purified. Different specimens afforded acetyl chloride and boric oxide in almost quantitative yield. Chlorine easily hydrolysed by cold water is indicated by " e.h."

Fission of Primary Alkyl Acetates.—Ethyl acetate (13·25 g.) in *n*-pentane (180 c.c.) gave a precipitate of *ethyl acetate–boron trichloride complex* (28·1 g., 91%), m. p. 43—47° (Found: Cl, 50·9; B, 5·24. $C_4H_8O_2Cl_3B$ requires Cl, 51·8; B, 5·28%), which was filtered off at 20° and dried at 20°/10 mm. At 82° it decomposed as described.[1] It was vigorously decomposed by water (3 mols.) to ethyl acetate, boric acid, and hydrogen chloride. Similarly *n*-butyl acetate (9·42 g.) in *n*-pentane (40 c.c.) gave a precipitate (17·8 g., 94%) of the complex, m. p. 25—26° (Found: Cl, 44·4; B, 4·43. Calc. for $C_6H_{12}O_2Cl_3B$: Cl, 45·7; B, 4·64%). To a suspension of the complex (7·77 g., 1 mol.) in *n*-pentane (20 c.c.) pyridine (2·36 g., 1 mol.) in *n*-pentane (20 c.c.) was added at 20°. Pyridine–boron trichloride complex (6·26 g., 97·5%), m. p. 113—114°, was filtered off, and *n*-butyl acetate (3·21 g., 83%), b. p. 122—124°, n_D^{22} 1·3925, was recovered. With water the complex was violently hydrolysed to the original ester, hydrogen chloride, and boric

[5] Gerrard and Wheelans, *Chem. and Ind.*, 1954, 758.

acid. On destructive distillation the complex (17·8 g.) afforded a cold-trap condensate (7·84 g.), *n*-butyl dichloroboronite (7·0 g., 59%), b. p. 34°/12 mm., n_D^{20} 1·4135, d_4^{16} 1·066 (Found: Cl, 42·7; B, 6·82. Calc. for $C_4H_9OCl_2B$: Cl, 45·8; B, 6·99), and a brown solid (2·76 g.) (Found: Cl, 30·8; B, 10·0; OAc, 15·5%). To the condensate (Found: e.h. Cl, 36·4%) aniline was added; *n*-butyl chloride (1·0 g., 15%), b. p. 76°, n_D^{18} 1·3970, was withdrawn at 80°/14 mm., and acetanilide (3·96 g., equiv. to AcCl in 38·4% yield) remained after removal of base hydrochloride with water.

The *o*-nitrophenyl acetate complex (24·8 g.), an orange-red precipitate from methylene dichloride (60 c.c.), decomposed as it melted at about 0°. Volatile matter was removed at 20°/0·5 mm. and trapped at −80°, leaving the bright-red crystalline *o*-nitrophenyl dichloroboronite (18·41 g.), m. p. 63° (Found: Cl, 31·3; B, 5·08. Calc. for $C_8H_4O_3NCl_2B$: Cl, 32·3; B, 4·93%), which (5·29 g., 1 mol.) in benzene (40 c.c.) gave with pyridine (1·90 g., 1 mol.) the pink voluminous precipitate of the base–dichloroboronite complex (7·18 g. Calc., 7·19 g.), m. p. 160° (Found: Cl, 23·5; B, 3·70; C_5H_5N, 26·3. Calc. for $C_{11}H_9O_3N_2Cl_2B$: Cl, 23·7; B, 3·62; C_5H_5N, 26·4%). With aniline the trapped volatile matter afforded acetanilide (9·99 g., 89%), m. p. 114°.

The complex from 2-chloroethyl acetate (9·82 g.) had m. p. 40—50° and decomposed at 87°, giving a distillate (4·94 g.), b. p. 48—51° (Found: e.h. Cl, 53·3; B, 1·44%; equiv. to BCl_3, 0·80 g., and AcCl, 3·98 g.), which afforded acetyl chloride (3·2 g.), b. p. 52° (Found: Cl, 45·5. Calc. for C_2H_3OCl: Cl, 45·2%). The condensate in the trap also contained boron trichloride (0·41 g.) and acetyl chloride (0·17 g.). The residue (12·6 g.) from the primary distillation comprised dichloroboronite, chloroboronate, and undecomposed complex. To further the disproportionation to trialkyl borate, the residue was heated at 160°/10 mm. for 2 hr. The trap (−80°) contained boron trichloride (1·71 g.) and acetyl chloride (1·41 g.), and the residue gave a mixture (3·93 g.) of chloroboronate and borate, b. p. 75—77°/0·6 mm. (Found: e.h. Cl, 14·9; B, 4·82%), and tri-2-chloroethyl borate (1·28 g.), b. p. 92°/0·5 mm. (Found: B, 4·36. Calc. for $C_6H_{12}O_3Cl_3B$: B, 4·34%).

The somewhat soluble 2 : 2 : 2-*trichloroethyl acetate–boron trichloride complex* (21·4 g., 78%), m. p. 19° (Found: e.h. Cl, 34·9; B, 3·32. $C_4H_6O_2Cl_6B$ requires e.h. Cl, 34·6; B, 3·51%), was precipitated as a white solid from *n*-pentane (250 c.c.) by the acetate (17·15 g.). At 25° it slowly decomposed (2·5 hr.), affording at 30 mm. a condensate (4·01 g.) which yielded boron trichloride (1·02 g.) and acetyl chloride (2·80 g.) (Found: Cl, 45·3%), and as residue (9·25 g.) (Found: e.h. Cl, 19·5; B, 3·22%) a mixture of the dichloroboronite and chloroboronate, which (8·6 g.) on being heated under reflux for 3 hr. at 150°/40 mm. gave a condensate (0·43 g.) at −80° and tris-2 : 2 : 2-trichloroethyl borate (5·86 g.), b. p. 134—136°/0·4 mm., m. p. 89° (Found: C, 15·9; H, 2·2; Cl, 69·7; B, 2·51. Calc. for $C_6H_6O_3Cl_9B$: C, 15·8; H, 1·3; Cl, 69·9; B, 2·38%).

The complex from *n*-octyl acetate (12·9 g.) gave no trap-condensate at 15°/30 mm. (45 min.) or at 50°/30 mm. (15 min.), but did so slowly at 80°/30 mm., and more rapidly at 90°/30 mm. The residue afforded *n*-octyl chloride (8·9 g.), b. p. 65—69°/18 mm. (Found: Cl, 23·7. Calc. for $C_8H_{17}Cl$: Cl, 23·9%), and a residue (4·68 g.). The condensate (8·0 g.) (Found: Cl, 52·7; B, 2·23%) comprised boron trichloride (1·95 g.) [separated as pyridine–boron trichloride complex (Found: Cl, 53·9. Calc. for $C_5H_5NCl_3B$: Cl, 54·2%)] and acetyl chloride (5·4 g.) (Found: Cl, 45·7%).

Benzyl acetate (10·0 g.) gave a complex which decomposed vigorously at 0°. Acetyl chloride (Found: Cl, 44·8%) and boron trichloride (Found: Cl, 90·0; B, 9·45. Calc. for Cl_3B: Cl, 90·8; B, 9·20%) were obtained by distillation in amounts equivalent to quantitative decomposition of the complex. Instead of the expected benzyl chloride, however, the residue (7·32 g.), which was not volatile at 200°/0·2 mm., afforded boric acid (2·1 g.) and a polymer (Found: C, 91·5; H, 6·8%; *M*, 2330, by cryoscopy in benzene), the latter being extracted by benzene. Benzyl chloride was not obtained on interaction of benzyl alcohol (3·97 g., 1 mol.) and boron trichloride (1 mol.). Hydrogen chloride continued to be evolved beyond the 1 mol. stage as the temperature was raised from −80° to 15°, and after 2 days a brown glass (2·04 g.), m. p. 58—60° (Found: C, 91·8; H, 6·7%), was obtained from the benzene extract of the residue. Although benzyl chloride is itself converted into a rubbery substance by boron trichloride at 20°, the process is slow and the product is insoluble in benzene.

*iso*Butyl acetate (6·94 g.) afforded the complex (m. p. 36°) which decomposed vigorously at 98° and gave hydrogen chloride (0·835 g.), a condensate (8·29 g.), and a charred residue (3·67 g.) (Found: Cl, 19·0; AcO, 7·9%). Pyridine (6·3 g.) was added to the condensate at −80°, and a mixture (3·66 g.) of *tert.*-butyl chloride (75%, by hydrolysis with cold 3N-nitric acid) and *iso*butyl chloride (25%, by total chlorine content) (Found: Cl, 38·2. Calc. for C_4H_9Cl:

Cl, 38·3%) was withdrawn at low pressure, leaving a mixture of pyridine–acetyl chloride compound (equiv. to AcCl, 4·07 g., by determination of e.h. Cl) and pyridine–boron trichloride complex (1·14 g., equiv. to BCl_3, 0·68 g.) (insoluble in water). The complex from *neo*pentyl acetate (9·61 g.) behaved very similarly, affording a mixture (5·03 g.), b. p. 82—90°, of (mainly) *tert.*-amyl chloride (Found : e.h. Cl, by 3N-nitric acid at 20°, 31·5%) and *neo*pentyl chloride (Found : total Cl, 32·9. Calc. for $C_5H_{11}Cl$: Cl, 33·2%).

Fission of Ethyl Esters of Other Acids.—The complex from the *n*-butyrate (9·00 g.) melted at 10°, but during 30 min. at 110° afforded no condensate. The distillate (16·55 g.), b. p. 89—94°, comprised ethyl dichloroboronite (7·86 g.) and *n*-butyryl chloride (7·05 g.), the proportions being computed from the determination of e.h. chlorine (42·6%), boron (4·06%), and butyric acid, but the condensate at −80° weighed only 0·06 g. The dichloroboronite was remarkably stable in the presence of butyryl chloride, and it was only after long heating under reflux that a pure specimen (Found : Cl, 33·4. Calc. for C_4H_7OCl : Cl, 33·3%) of butyryl chloride (anilide, m. p. 90°) was obtained.

The complex from the trimethylacetate (12·70 g.) was heated at 120° to effect steady decomposition. Protracted distillations (b. p. 78—102°) and analyses showed the presence of ethyl dichloroboronite (11·10 g., 89·6%) and trimethylacetyl chloride (10·64 g., 94%). A specimen (2·52 g.) of trimethylacetyl chloride, b. p. 101—102° (Found : e.h. Cl, 28·8. Calc. for C_5H_9OCl : Cl, 29·4%) (anilide, m. p. 129°), was eventually obtained. There was no condensate in the trap.

The complex from the dichloroacetate (8·12 g.) melted with decomposition and dissociation at 40—45°. The condensate (5·38 g.) (Found : e.h. Cl, 78·6; B, 8·4%) at −80° comprised boron trichloride (4·68 g.) [pyridine–boron trichloride complex (4·52 g.), m. p. 115° (Found : Cl, 53·8%)] and ethyl chloride (0·70 g.), and the residue afforded a mixture (7·36 g.) (Found : e.h. Cl, 4·7%) of dichloroacetyl chloride (1·43 g.) (anilide, m. p. 119—120°) and ethyl dichloroacetate (5·93 g.). The latter was separated in part (2·6 g.), b. p. 146—148°, n_D^{20} 1·4380 (Found : Cl, 45·6. Calc. for $C_4H_6O_2Cl_2$: Cl, 45·2%), by protracted fractionation.

Ethyl trichloroacetate (15·50 g.) gave a mobile liquid which was evidently not a complex. On distillation ethyl trichloroacetate (88·5% recovery), b. p. 62°/16 mm. (Found : Cl, 55·2. Calc. for $C_4H_5O_2Cl_3$: Cl, 55·6%), a condensate of boron trichloride (97·5% recovery) (Found : e.h. Cl, 89·0; B, 9·0%), and a black liquid residue (1·16 g.) (Found : e.h. Cl, 0; B, 5·36%) were obtained. Of the 6·70 g. of boron trichloride used in a second experiment, 6·07 g. were removed in 2·5 hr. at −80°/0·3 mm.

The benzoate (11·90 g.) gave a complex [no trap-condensate at 20°/20 mm.] which melted at 40°, decomposed at 60°/20 mm., giving a condensate (8·89 g.) (Found : e.h. Cl, 72·0; B, 8·44%) comprising ethyl dichloroboronite (1·90 g.), b. p. 36°/140 mm. (Found : e.h. Cl, 56·5; B, 8·10. Calc. for $C_2H_5OCl_2B$: Cl, 55·9; B, 8·54%), and boron trichloride (5·3 g.). At *ca.* 98°/20 mm. a mixture (10·62 g.) (Found : e.h. Cl, 10·9%) of benzoyl chloride (4·5 g., separated as anilide, m. p. 162°) and ethyl benzoate (4·2 g.), b. p. 105°/24 mm. (Found : equiv., 150. Calc. : equiv., 150·2), remained.

Fission of n-*Butyl Formate.*—The formate (5·45 g.) formed a complex which liquefied at *ca.* 15°. It was warmed from 40° to 65° under an upright condenser kept at 9° : hydrogen chloride (1·50 g.), carbon monoxide (1046 c.c. at N.T.P., 87%) and a trap-condensate (2·52 g.) (Found : e.h. Cl, 52·5%) of *n*-butyl chloride and boron trichloride (1·46 g.) [pyridine complex, m. p. 114° (Found : Cl, 53·4; C_5N_5N, 41·0%)] were obtained. The remainder afforded *n*-butyl chloride (2·8 g.), b. p. 76° (Found : Cl, 38·2%), and a black solid (2·17 g.) (Found : Cl, 11·3; B, 15·4%). When the decomposition was carried out at 50—55°/40 mm. impure *n*-butyl dichloroboronite (3·35 g.), b. p. 51°/40 mm. (Found : Cl, 47·1. Calc. for $C_4H_9OCl_2B$: Cl, 45·8%), was isolated and hydrogen chloride (1·92 g.) was absorbed in alkali after passing the cold trap.

Fission of Acetates of Secondary Alcohols.—*sec.*-Butyl acetate (6·63 g.) gave the complex which melted below 0°, but no trap-condensate was formed at 20° (2 hr.) or at 20°/50 mm. At 50°/50 mm. there was a condensate (6·38 g.) and a residue (6·05 g.) (Found : e.h. Cl, 38·3; B, 9·03; AcO, 32·6%) containing 88·5% of the boron in the system. The condensate comprised *sec.*-butyl chloride (4·0 g.) (isolated after treatment with pyridine), b. p. 66—67° (Found : Cl, 38·0%), acetyl chloride (2·1 g.), and boron trichloride (0·2 g.), estimated by means of pyridine–acetyl chloride and pyridine–boron trichloride complexes. When a 2 : 1 molar ratio of ester (14·13 g.) and boron trichloride was used, the mixture was entirely liquid at 20° and distillation afforded acetyl chloride (2·53 g.), *sec.*-butyl chloride (3·97 g.), but-2-ene (1·05 g.) [converted into 2 : 3-dibromobutane (Found : C, 22·4; H, 4·0; Br, 73·8. Calc. for $C_4H_8Br_2$: C, 22·2; H, 3·71; Br, 74·1%)], hydrogen chloride (0·65 g.), *sec.*-butyl acetate (3·52 g.), and a solid (6·06 g.)

(Found : e.h. Cl, 28·7; B, 9·3; AcO, 53·5%). When the primary liquid [ester (17·24 g., 2 mols.) and boron trichloride (8·70 g., 1 mol.)] was allowed to remain at 21° for 22 hr. instead of being distilled, crystals of *dichlorodiacetyl diborate* separated (4·63 g.), were filtered off, and were washed with *n*-pentane (Found : Cl, 31·2; B, 9·09; AcO, 51·2. $C_4H_6O_5Cl_2B_2$ requires Cl, 31·3; B, 9·55; AcO, 52·1%). This compound (3·26 g., 1 mol.), mixed with acetic acid (1·73 g., 2 mols.) in methylene dichloride (30 c.c.) at 20°, evolved hydrogen chloride (0·89 g., 1·7 mol.), and on removal of the solvent (finally at 60°/16 mm.) tetra-acetyl diborate (3·82 g., 97%) (Found : B, 7·75; AcO, 85·6. Calc. for $C_8H_{12}O_9B_2$: B, 7·90; AcO, 86·3%) remained. The dichloro-compound (9·17 g.) began to decompose about 150° and gave acetyl chloride (5·59 g.), b. p. 50—52° (Found : Cl, 45·2%), whereas all the boron remained as impure oxide in a coke-like residue (2·94 g.) (Found : B, 28·0%). There was no melting.

When 3 mols. of ester (19·95 g.) were used with 2 mols. of boron trichloride (13·41 g.) the liquid slowly deposited crystals at 23°. After 5 days the condensate at −80° weighed 3·14 g., increasing to 3·29 g. during the next 2 days. The effluent comprised butene (1·0 g.) and hydrogen chloride (0·776 g.); further volatilisation of the condensate afforded a residue (1·98 g.) which was added to the condensate obtained as follows. From the main residue volatile matter was removed at 23°/20 mm., finally at 65°/20 mm., affording a condensate (13·64 g., total, 15·62 g.) (Found : e.h. Cl, 10·7; total Cl, 36·8%) comprising acetyl chloride (3·5 g.) (converted into the anilide) and *sec.*-butyl chloride (7·5 g.), b. p. 68° (Found : Cl, 37·6%) (isolated after treatment with aniline), and a solid residue (12·94 g. Calc. for dichlorodiacetyl diborate : 12·98 g.) (Found : Cl, 31·2; B, 9·06; AcO, 51·2%). From an acetate having α_D^{21} −6·46° (*l* 1 dm.) (ROH, α_D^{27} −3·28°), *sec.*-butyl chloride having α_D^{26} +4·89° (*l* 1 dm.), n_D^{20} 1·3955, d_4^{20} 0·865, was obtained.

Similarly *iso*propyl acetate (16·3 g., 3 mols.) and boron trichloride (12·47 g., 2 mols.) also gave the diacetyl diborate (9·65 g.) (Found : Cl, 31·7; B, 8·72; AcO, 50·9%); *iso*propyl chloride (7·08 g.), b. p. 36° (Found : Cl, 44·5. Calc. for C_3H_7Cl : Cl, 45·2%) was isolated; and acetyl chloride (3·4 g.) and boron trichloride (0·32 g.) were present in the volatile part.

(−)-1-Methylheptyl acetate (10·60 g., 3 mols.), α_D^{20} −5·87° (from ROH, α_D^{20} −7·99°; *l* 1 dm.), and boron trichloride (4·81 g., 2 mols.) in *n*-pentane (30 c.c.) afforded dichlorodiacetyl diborate (3·47 g.) (Found : Cl, 31·5; B, 9·02; AcO, 52·1%) which was filtered off after the mixture had been warmed at 60° for 20 hr. Distillation of the filtrate afforded acetyl chloride (0·76 g.) (as anilide, 1·31 g.), octene (0·75 g.) (as octene dibromide, 1·40 g.), b. p. 107°/12 mm., and (+)-1-methylheptyl chloride (6·46 g.), b. p. 66°/15 mm., α_D^{25} +21·92° (*l* 1 dm.) n_D^{20} 1·4270 (Found : Cl, 23·7. Calc. for $C_8H_{17}Cl$: Cl, 23·9%).

(−)-1 : 2 : 2-Trimethylpropyl acetate (9·87 g., 3 mols.) (α_D^{20} −6·20°, *l* 1 dm.) and boron trichloride (2 mols.) gave the diborate (5·20 g.) (Found : Cl, 31·7; B, 8·94; AcO, 48·0%), an optically inactive mixture (7·2 g.), b. p. 110—112° (almost entirely *tert.*-chloride), a little 1 : 2 : 2-trimethylpropyl chloride (Found : e.h. Cl, by 3N-nitric acid at 20°, 28·3; total Cl, 29·6. Calc. for $C_6H_{13}Cl$: Cl, 29·5%), and acetyl chloride (1·13 g.).

Fission of tert.-*Butyl Acetate*.—Several experiments under different conditions and with different proportions of reagents indicated a general similarity with the *sec.*-butyl acetate systems. With 3 mols. of acetate (9·31 g.) and 2 mols. of the trichloride, the complex began to decompose at about −25°. After 14 hr. at 20°, volatile matter was withdrawn at 40°/30 mm., leaving the diacetyl diborate (6·78 g.). The condensate (8·33 g.) comprised acetyl chloride, removed by water, and *tert.*-butyl chloride (5·45 g.), b. p. 50—52° (Found : Cl, 38·7. Calc. for C_4H_9Cl : Cl, 38·3%). Dropwise addition of the acetate (5·16 g., 3 mols.) in *n*-pentane to boron trichloride (3·47 g., 2 mols.) in *n*-pentane (20 c.c.) at −10° immediately precipitated white crystals of dichlorodiacetyl diborate (3·45 g., 100%) (Found : Cl, 31·3; B, 8·99; AcO, 52·4%) which were filtered off, washed with *n*-pentane, and dried at 20 mm. With aniline the filtrate afforded acetanilide (1·16 g.), m. p. 114°.

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828. *Curvularin. Part I. Isolation and Partial Characterisation of a Metabolic Product from a New Species of* Curvularia.

By O. C. Musgrave.

The isolation of a new mould metabolic product, $C_{16}H_{20}O_5$, from a species of *Curvularia* is described; a second compound, $C_{16}H_{18}O_5$, is also obtained in minor amount. The compound $C_{16}H_{20}O_5$, for which the name "curvularin" is proposed, is shown by chemical and spectroscopic studies to contain two *C*-methyl groups, a dihydroxybenzoyl system, and an aliphatic carbonyl group.

During an examination in 1952 of the metabolic products of a number of moulds, C. T. Calam [1] isolated a crystalline compound, m. p. 201—203°, from the culture filtrate of a species of *Curvularia*. As there is no record of any previous investigation of the chemistry of the metabolic products of this genus a detailed examination of the compound was considered desirable. Through the courtesy of Dr. Calam, to whom I am glad to express my thanks, a culture of the mould and a specimen of the metabolic product were made available for further work. The mould was identified as a species of *Curvularia* at the Commonwealth Mycological Institute at Kew; it does not appear to have been described previously. Although when first isolated the mould produced spores, it later lost this capacity.

The *Curvularia* was grown on a medium containing glucose, peptone, and mineral salts. Ether-extraction of the culture filtrate afforded a solid (0·40—0·48 g./l.) which on crystallisation gave in high yield a compound $C_{16}H_{20}O_5$, m. p. 206—206·5°, $[\alpha]^{18}$ −36·3°, identical with that isolated by Calam. The name "curvularin" is proposed for this substance which has not been described previously. Curvularin contains two *C*-methyl groups and two active hydrogen atoms which are present in two hydroxyl groups. It exhibits strong infrared absorption at 3356 cm.$^{-1}$ (hydroxyl) and forms a crystalline dibenzoate, $C_{30}H_{28}O_7$, a crystalline di-*p*-chlorobenzoate, $C_{30}H_{26}O_7Cl_2$, and an amorphous diacetate, $C_{20}H_{24}O_7$, the spectra of which do not show this band. Curvularin possesses the properties of a phenol, giving a purple ferric reaction in aqueous ethanol, coupling with diazotised aniline in alkaline solution to give a red dye, and dissolving readily in aqueous alkali, from which it is precipitated unchanged by carbon dioxide. Treatment with ethereal diazomethane or dimethyl sulphate and potassium carbonate readily gives a dimethyl ether, $C_{18}H_{24}O_5$, showing that both hydroxyl groups are phenolic. The molecular formula of curvularin permits of the presence of only one benzene nucleus and hence both hydroxyl groups must be attached to this. The formulation of the compound as a dihydric phenol explains *inter alia* the sensitivity of its alkaline solutions to aerial oxidation. Curvularin fails to decolorise a solution of 2 : 6-dichlorophenolindophenol, showing that it does not contain a quinol grouping; this is confirmed by the blue colour developed in alkaline solution with 2 : 6-dichloroquinone chloroimide [2] which indicates the presence of an unsubstituted position on the aromatic ring *para* to an hydroxyl group. The hydroxyl groups must therefore be *ortho* or *meta* to one another. Curvularin reacts with diazoaminobenzene, giving bisphenylazocurvularin, $C_{28}H_{28}O_5N_4$, which implies that at least two hydrogen atoms are attached directly to the benzene nucleus.

Chemical tests have failed to indicate the functions of the three remaining oxygen atoms in the curvularin molecule. Thus both curvularin and *OO*-dimethylcurvularin give a negative reaction in the hydroxamic acid test for the carboxylic ester group and do not give ketonic derivatives under the usual conditions. However, the infrared absorption spectra of these compounds show clearly the presence of two different types of carbonyl group. Curvularin exhibits three strong absorption bands in the 6 μ region, at 1692, 1653, and 1606 cm.$^{-1}$, which in *OO*-dimethylcurvularin are found at 1736, 1695, and 1618 cm.$^{-1}$. The lower frequencies for curvularin are due presumably to hydrogen-bonding between

[1] Calam, unpublished work in Imperial Chemical Industries Limited, Pharmaceuticals Division.
[2] Gibbs, *J. Biol. Chem.*, 1927, **72**, 649.

the carbonyl and hydroxyl groups which is known [3] to result in the lowering of carbonyl frequencies by *ca.* 50 cm.$^{-1}$. Because of this complication the absorption spectrum of curvularin is unsuitable for diagnostic purposes. In *OO*-dimethylcurvularin, however, hydrogen-bonding cannot be present and the absorption bands can be assigned to specific groups with some confidence. The band at 1736 cm.$^{-1}$ is attributed to an aliphatic carbonyl group, several types of which show similar absorption (*e.g.*, unconjugated five-membered ring ketone, 1745 cm.$^{-1}$; unconjugated ester, 1740 cm.$^{-1}$; unconjugated six-membered ring lactone, 1740 cm^{-1}).[4] Because of the lack of further information concerning this carbonyl group, no conclusion can be drawn as to its exact nature. The band at 1692 cm.$^{-1}$ appears to be due to a ketonic group conjugated with the benzene ring, as alkyl aryl ketones are known [4] to absorb at *ca.* 1690 cm.$^{-1}$. The band at 1618 cm.$^{-1}$ is attributed to the absorption of the conjugated aromatic system and is similar to the intense bands in the 1580—1620 cm.$^{-1}$ region shown by many alkoxyphenyl ketones. The absorption of curvularin diacetate in the 6 μ region resembles that of the dimethyl ether. Strong absorption bands are found at 1770 (phenolic acetate), 1727 (aliphatic carbonyl), 1695 (aromatic ketone), and 1621 cm.$^{-1}$ (conjugated aromatic system). From the above chemical and spectral evidence it appears that the dihydroxybenzoyl system $\cdot C_6H_2(OH)_2CO\cdot$ is present in curvularin.

The ultraviolet absorption spectrum is of the type expected from such a chromophore and reduction experiments provide chemical evidence in favour of it. Deoxydihydrocurvularin, $C_{16}H_{22}O_4$, can be isolated on the hydrogenation of curvularin in acetic acid with Adams catalyst, if the reaction is interrupted after the uptake of two mols. of hydrogen. The infrared spectrum of this compound in the 6 μ region shows one strong band at 1704 cm.$^{-1}$ (hydrogen-bonded aliphatic carbonyl group) and only weak absorption in the 1600 cm.$^{-1}$ region, indicating that the carbonyl group conjugated with the aromatic ring has been lost, presumably by reduction to a methylene group. The ultraviolet spectrum is quite unlike that of curvularin and bears a marked resemblance to that of resorcinol (see Table).

Ultraviolet absorption spectra (in ethanol).

Resorcinol	$\lambda_{max.}$ 2200 (ε 6100), 2760 Å (ε 2150)
Deoxydihydrocurvularin	$\lambda_{infl.}$ 2260 Å (ε 7850); $\lambda_{max.}$ 2860 Å (ε 2850)
Sodium borohydride product	$\lambda_{infl.}$ 2240 Å ($E^{1\%}_{1\,cm.}$ 280); $\lambda_{max.}$ 2850 Å ($E^{1\%}_{1\,cm.}$ 90)

The reduction of curvularin by sodium borohydride in methanol (a specific reagent for the reduction of aldehydes and ketones [5]) gives an amorphous product, the ultraviolet spectrum of which resembles that of deoxydihydrocurvularin. In this case the aromatic carbonyl group has presumably been converted into a secondary alcohol.

After the separation of curvularin from the crude metabolic product a second compound, $C_{16}H_{18}O_5$, m. p. 224·5—225°, $[\alpha]_D^{18}$ −83°, can be isolated in small quantity. It contains two hydroxyl groups and, as it is soluble in aqueous sodium hydroxide but insoluble in aqueous sodium hydrogen carbonate and gives an orange dye on treatment with diazotised aniline in alkaline solution, it is phenolic. The presence of an unsubstituted *para*-position on the aromatic ring is shown by the positive reaction with 2 : 6-dichloroquinone chloroimide. Like curvularin the compound fails to react with carbonyl reagents and gives a negative reaction in the hydroxamic acid test for the carboxylic ester group, but the infrared spectrum reveals two types of carbonyl group. Strong absorption bands are found at 1718 (probably aliphatic carbonyl), 1623 (hydrogen-bonded aromatic carbonyl), and 1592 cm.$^{-1}$ (conjugated aromatic system). The compound therefore contains a hydroxybenzoyl group. Its solution in alkali is deep yellow in colour and, unlike such a solution of curvularin, appears to be unaffected by oxygen.

Experimental

Analyses are by the microanalytical laboratory of this Department; molecular weights were determined ebullioscopically in acetone. Ultraviolet absorption spectra were determined with a Hilger "Uvispek" spectrophotometer. Infrared absorption spectra were determined,

[3] Gordy, *J. Chem. Phys.*, 1940, **8**, 516.
[4] Grove and Willis, *J.*, 1951, 877.
[5] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.

for Nujol mulls, with a double-beam spectrophotometer with rock-salt optics; the concentrations and thickness of the mulls were not measured.

Cultural Conditions.—The *Curvularia* (No. F334 in the Nobel Division culture collection; Commonwealth Mycological Institute Cat. No. I.M.I. 52,980) was grown on beer wort-agar slopes at 25° for 14 days, a thick growth of dark-grey, non-sporing mycelium being obtained. A suspension of mycelial fragments in sterile water was used for inoculation of aqueous media. The *Curvularia* showed but poor growth on media containing only glucose and mineral salts; vigorous growth resulted when an amino-acid source was added. A suitable medium contained glucose (400 g.), "Bactopeptone" (100 g.), magnesium sulphate (5 g.), dipotassium hydrogen phosphate (5 g.), and traces of ferrous, zinc, copper, and manganese sulphates and ammonium molybdate in tap water (20 l.). The cultures were grown at 24° in "Glaxo" bottles each containing 400 ml. of medium. The glucose concentration of the solution fell rapidly after 4 days and after 14 days was 1—3 g./l. The upper surface of the mycelium was then light grey with some white secondary growths, and the reverse was black.

Isolation of Curvularin.—The culture filtrate was decanted from the mycelium (dry wt. *ca.* 7·5—9·0 g./l.). Manual extraction of the culture filtrate (10 vol.) with ether (3 × 1 vol.) gave, after removal of the solvent, crude curvularin as colourless or pale yellow-brown crystals. Initially the yield of crude solid was found to vary widely from batch to batch. The culture of *Curvularia* then employed was observed to give rise to two types of mycelium when grown on aqueous media: a light grey form which produced curvularin, and a dark grey, faster-growing form which produced only traces of the substance; morphologically the strains appeared to be identical. Cultures prepared from the light grey strain were used in subsequent experiments and consistently high yields of crude curvularin (0·40—0·48 g./l. of the culture filtrate) were obtained.

Crude curvularin (7·03 g.) was dissolved in hot benzene containing a small quantity of methanol, and the solution was boiled until crystallisation began and then set aside. *Curvularin* (5·09 g.) separated as plates, m. p. 206—206·5° (Pyrex or evacuated soda-glass capillary), $[\alpha]_D^{18}$ −36·3° (*c* 3·8 in EtOH) [Found: C, 65·9, 65·8, 65·9; H, 6·9, 6·9, 6·8; *C*-Me (Kuhn–Roth), 7·5; active H (Zerewitinoff), 0·57; OH (by acetylation), 11·95%; *M*, 307. $C_{16}H_{20}O_5$ requires C, 65·75; H, 6·9; 2*C*-Me, 10·3; 2 active H, 0·68; 2OH, 11·65%; *M*, 292·3], ultraviolet absorption max. in (*a*) EtOH at 2230, 2720, and 3045 Å (ε 11,300, 6350, and 5100) and inflection at 2290 Å (ε 10,150), unaffected by the addition of hydrochloric acid, and (*b*) 0·005N-aqueous sodium hydroxide at 2330 and 3510 Å (ε 10,200 and 9300) and inflections at 2580 and 3280 Å (ε 7250 and 8100). Concentration of the mother-liquor from the above crystallisation gave more crystalline material (0·93 g.), m. p. 202—203°, which on recrystallisation afforded curvularin (0·62 g.), the total yield being 5·71 g. (81%).

Curvularin is soluble in ethanol, methanol, dioxan, acetone, pyridine, and concentrated sulphuric acid, moderately soluble in acetic acid and ether, and sparingly soluble in benzene, light petroleum, chloroform, and water. It gives yellow solutions with aqueous ammonia, sodium carbonate, and sodium hydroxide, from which it may be recovered unchanged by acidification. Alkaline solutions of curvularin darken rapidly in air, eventually becoming purple. This sensitivity to oxygen in the presence of alkali is also demonstrated by the rapid decomposition of curvularin at its m. p. when heated in open soda-glass capillaries. Curvularin does not contain nitrogen, sulphur, or halogen (Lassaigne test) or methoxyl groups (Zeisel). It is recovered unchanged after 3 hours' refluxing with 2N-sulphuric acid in aqueous ethanol. Heating with 58% aqueous hydriodic acid results in decomposition. Curvularin decolorises bromine in dioxan and potassium permanganate in acetone. With tetranitromethane in ethanol it gives a deep yellow colour, as do many other phenolic compounds. It readily reduces warm Fehling's solution but not ammoniacal silver nitrate solution. It reduces Tollens's reagent only if warmed; a silver mirror is formed immediately in the cold, however, if curvularin is first warmed with alkali. There is no uptake of hydrogen when a solution in acetic acid is shaken with a palladium catalyst, indicating the absence of simple olefinic unsaturation. The 3 : 5-dinitrobenzoic acid–aqueous-ethanolic alkali test for the ketomethylene group is negative. Neither curvularin nor the culture filtrates from *Curvularia* show anti-bacterial activity (against *B. subtilis*, *B. coli*, and *Staph. aureus*) or antifungal activity (spore germination test with *P. digitatum*).

Esters.—A mixture of curvularin (0·30 g.), dry pyridine (5 ml.), and acetic anhydride (5 ml.) was kept for 7 days at room temperature. Working up in the usual manner gave a gum (0·35 g.) which did not crystallise from solvents and on distillation in a short-path still at 160°/0·08 mm. gave curvularin diacetate as a pale yellow glass which softened at *ca.* 50° (Found: C, 65·3;

H, 6·7; Ac, 21·1%; *M*, 395. Calc. for $C_{20}H_{24}O_7$: C, 63·8; H, 6·45; 2Ac, 22·9%; *M*, 376·4), ultraviolet absorption inflection in EtOH at 2350 Å (ε 5600). Consistent C and H analyses could not be obtained for this compound. The infrared absorption spectrum was determined on a thin film of the compound.

A mixture of curvularin (0·50 g.), dry pyridine (10 ml.), and benzoic anhydride (2 g.) was kept at room temperature for 8 days. Working up in the usual manner gave an oil which was dissolved in benzene to which was added light petroleum (b. p. 60—80°) to turbidity. *Curvularin dibenzoate* (0·30 g.) separated as needles, m. p. 133—134°, $[\alpha]_D^{18}$ −10·8° (*c* 1·9 in $CHCl_3$) (Found: C, 72·05; H, 5·9. $C_{30}H_{28}O_7$ requires C, 72·0; H, 5·65%), ultraviolet absorption max. in EtOH at 2360 Å (ε 36,700), inflection at 2740 Å (ε 4400).

A solution of curvularin (0·20 g.) in aqueous sodium hydroxide (10%, 2 ml.) was shaken under nitrogen with benzoyl chloride (0·5 ml.). Cooling and scratching afforded a solid which on crystallisation from ethanol gave curvularin dibenzoate as needles, m. p. and mixed m. p. 132—133°.

Curvularin (0·50 g.), dry pyridine (10 ml.), and *p*-chlorobenzoic anhydride (1·5 g.) were warmed to effect dissolution and kept at room temperature for 5 days. Working up in the usual manner afforded the *di-p-chlorobenzoate* (0·73 g.) which crystallised from benzene–light petroleum (b. p. 60—80°) or from ethanol as felted needles, m. p. 152—153°, $[\alpha]_D^{18}$ −8·4° (*c* 2·1 in $CHCl_3$) (Found: C, 63·6; H, 4·8; Cl, 12·9%; *M*, 590. $C_{30}H_{26}O_7Cl_2$ requires C, 63·3; H, 4·6; Cl, 12·45%; *M*, 569·4).

OO-*Dimethylcurvularin*.—(*a*) Curvularin (20 g.) in dry acetone (300 ml.) was heated under reflux with potassium carbonate (60 g.) and dimethyl sulphate (60 ml.) during 1·5 hr. After evaporation under reduced pressure, the mixture was shaken with water and extracted with ether, evaporation of which gave a yellow oil (22 g.). Distillation of a portion of this material in a short-path still at 170—180°/0·08 mm. gave a pale yellow glass which crystallised. The remainder of the oil crystallised from aqueous ethanol when seeded, giving OO-*dimethylcurvularin* (19·06 g.) as short rods, m. p. 72°, $[\alpha]_D^{18}$ −2·9° (*c* 2·7 in $CHCl_3$) (Found: C, 67·5; H, 7·9; OMe, 19·6%; *M*, 333. $C_{18}H_{24}O_5$ requires C, 67·5; H, 7·55; OMe, 19·4%; *M*, 320·4), ultraviolet absorption max. in EtOH at 2230 and 2675 Å (ε 10,500 and 5100), inflection at 2910 Å (ε 3600). The infrared absorption spectrum was determined on a thin film of the compound.

(*b*) To a suspension of curvularin (2 g.) in dry ether (50 ml.) was added ethereal diazomethane [from *N*-nitrosomethylurea (10 g.), 40% aqueous potassium hydroxide (30 ml.), and ether (50 ml.)] and methanol [6] (0·1 ml.). After 2 days in the dark, the solution was filtered and evaporated, giving a yellow oil (2·17 g.). Crystallisation from aqueous ethanol (with seeding) gave *OO*-dimethylcurvularin, m. p. 70—71°, mixed m. p. 71·5—72°.

Bisphenylazocurvularin.—To a hot solution of curvularin (0·30 g.) in ethanol (10 ml.) was added a solution of diazoaminobenzene (0·60 g.) in the same solvent (5 ml.). After 2 days at room temperature, the crystalline precipitate was collected. Crystallisation from ethanol gave *bisphenylazocurvularin* (0·26 g.) as red blades, m. p. 232·5—233° (Found: C, 67·4; H, 5·7; N, 11·5%; *M*, 515. $C_{32}H_{30}O_5N_4$ requires C, 67·2; H, 5·65; N, 11·2%; *M*, 500·5).

Deoxydihydrocurvularin.—A solution of curvularin (1·0 g.) in acetic acid (100 ml.) was shaken with hydrogen at atmospheric pressure in the presence of prereduced Adams catalyst [7] (0·15 g.) until rather more than 2 mols. of hydrogen (153 ml. at N.T.P.) had been taken up. Evaporation of the filtered solution gave a semi-solid residue which on crystallisation from benzene–methanol gave *deoxydihydrocurvularin* (0·23 g.) as plates, m. p. 265·5—266° (evacuated Pyrex capillary) (Found: C, 69·4; H, 7·85%; *M*, 275. $C_{16}H_{22}O_4$ requires C, 69·05; H, 8·0%; *M*, 278·35).

Reduction of Curvularin with Sodium Borohydride.—A solution of curvularin (1·0 g.) in methanol (30 ml.) was neutralised by the addition of N-sodium hydroxide (6·9 ml.) and added during 10 min. to a solution of sodium borohydride (0·21 g.) in the same solvent (10 ml.), under nitrogen. After 3 hr. the solution was acidified and diluted with water. Ether-extraction gave a brown gum (0·95 g.).

Isolation of the Compound $C_{16}H_{18}O_5$.—The mother-liquors from the crystallisation of a number of batches of crude curvularin (49·5 g.), on further concentration, yielded a solid, m. p. 218° (1·84 g.). Crystallisation of this from ethyl acetate and then from benzene–methanol gave a *compound* as small octahedral prisms, m. p. 224·5—225° (decomp.), $[\alpha]_D^{18}$ −83° (*c* 3·0 in $COMe_2$) [Found: C, 66·7, 66·5; H, 6·4, 6·1; OH (by acetylation), 10·9%; *M*, 306. $C_{16}H_{18}O_5$

[6] Cf. Schönberg and Mustafa, *J.*, 1946, 746.
[7] Frampton, Edwards, and Henze, *J. Amer. Chem. Soc.*, 1951, **73**, 4432.

requires C, 66·2; H, 6·25; 2OH, 11·7%; *M*, 290·3], ultraviolet absorption max. in EtOH at 2250, 3015, and 3400 Å (ε 14,000, 5900, and 5950). The compound can also be purified slowly by sublimation at 200°/0·05 mm. It is moderately soluble in acetic acid, ethanol, methanol, ethyl acetate, and ether, and is sparingly soluble in chloroform, water, and benzene. It gives a brown ferric reaction in aqueous ethanol and decolorises a solution of potassium permanganate in acetone.

I am indebted to Mr. A. J. Baillie for supervising the growing of the *Curvularia*, to Dr. J. E. Gill for helpful discussion, and to Mr. R. Stewart for the determination of the infrared spectra.

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829. *The Preparation of Some Dimeric* sec.-*Aminoboron Dihalides.*

By O. C. MUSGRAVE.

A number of new *sec.*-aminoboron dihalides has been prepared. The formation of cyclic dimers by these compounds is limited to the products obtained from pyrrolidine, piperidine, and morpholine. In the other cases the steric effects of the substituents on the nitrogen atoms appear to prevent dimerisation.

THE rapid, spontaneous dimerisation of dimethylaminoboron dichloride, $Me_2\overset{+}{N}{=}\overset{-}{B}Cl_2$, was first observed in 1933 by Wiberg and Schuster.[1] Because of its low reactivity compared with that of the monomer, the crystalline dimer was assigned the cyclic structure (I) which has since received strong support from the small dipole moment found[2] for the compound. Later, dimethylaminoboron dibromide was found to undergo a similar, but much slower, dimerisation.[3,4] The corresponding ethyl compounds, diethylaminoboron dichloride and dibromide however failed to show any signs of dimerisation even after prolonged keeping;[3,4,5] no explanation has been put forward to account for this marked difference.

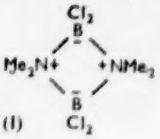
A number of aminoboron dihalides related to the above compounds has now been prepared from a variety of aliphatic secondary amines by J. F. Brown's method[6] in order to determine the factor controlling the dimerisation. The reaction of the amines with boron trihalides gave the addition compounds (II) which lost hydrogen halide on treatment with triethylamine. After removal of the precipitated triethylammonium halide, vacuum-distillation readily gave the *sec.*-aminoboron dihalides (III) as colourless fuming liquids. In this way the aminoboron dichlorides {III; X = Cl, $R_2 = -[CH_2]_4-$, $-[CH_2]_5-$, $O(CH_2{\cdot}CH_2-)_2$} were obtained from pyrrolidine, piperidine, and morpholine respectively, while the aminoboron dibromides (III; X = Br, $R_2 = -[CH_2]_4-$, $-[CH_2]_5-$) resulted from pyrrolidine and piperidine. The isolation of morpholinoboron dibromide from the reaction between morpholine, boron tribromide, and triethylamine did not prove to be possible. The product decomposed on attempted distillation owing, probably, to the fission of the morpholine ring by a reaction between the ether linkage and the boron dibromide group.[7]

Of the above compounds, 1-pyrrolidinyl-, piperidino-, and morpholino-boron dichloride quickly dimerised at room temperature, giving highly crystalline, sharp-melting solids. These are considered by analogy with Wiberg and Schuster's compound to have the bis-*spiro*cyclic structures (IV; X = Cl), (V; X = Cl), and (VI) respectively.

The dimerisation of 1-pyrrolidinylboron dibromide was markedly slower than that of

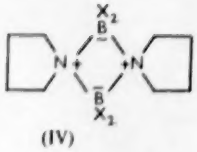
[1] Wiberg and Schuster, *Z. anorg. Chem.*, 1933, **213**, 89.
[2] C. A. Brown and Osthoff, *J. Amer. Chem. Soc.*, 1952, **74**, 2340.
[3] Wiberg, FIAT Review of German Science (1939—1946), Inorganic Chemistry, Vol. I (1948), p. 125.
[4] Goubeau, *op. cit.*, p. 215.
[5] Osthoff and C. A. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2378.
[6] J. F. Brown, *ibid.*, p. 1219.
[7] Cf. Benton and Dillon, *ibid.*, 1942, **64**, 1128.

the corresponding dichloride, while piperidinoboron dibromide had not dimerised completely after nine months at room temperature. These dimers are considered to have the structures (IV; X = Br) and (V; X = Br) respectively. All the above dimeric compounds, like the dimethylaminoboron dihalide dimers, are stable indefinitely in moist air and appear to be unaffected by water at 20°. Attempted crystallisation from benzene or chloroform however leads to partial decomposition on prolonged boiling of the solutions in contact with moist air. The molecular weights (determined ebullioscopically in benzene) of the morpholinoboron dichloride and piperidinoboron dibromide dimers show that some dissociation or decomposition of these compounds occurs in solution at 80°. The products from the reactions between boron trichloride and triethylamine with di-*n*-propylamine, di-*n*-butylamine, or 2-methylpiperidine showed no signs of dimerisation after six months at 20° and five days at 100°, and remained highly reactive liquids.

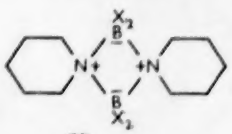


(I)

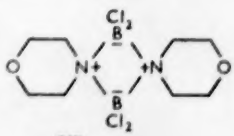
(II) (III)



(IV)



(V)



(VI)

The dimerisation of the aminoboron dihalides requires the formation of two N→B co-ordinate bonds, the strength of which is known to be highly dependent on the steric effects of the substituents on the nitrogen atom. Thus dimethylamine–trimethylboron [dissociation constant at 100° (K_{100}), 0·0214 atm.] is more stable than diethylamine–trimethylboron (K_{100}, 1·22 atm.), the lower stability of the latter being attributed to the greater steric effect of the ethyl groups. The replacement of the diethylamino-group by small heterocyclic rings which have much smaller steric requirements, as in pyrrolidine–trimethylboron (K_{100}, 0·0035 atm.) and piperidine–trimethylboron (K_{100}, 0·021 atm.), leads to a considerable increase in stability.[8] The co-ordinate bonds formed by tertiary amines are similar, triethylamine–trimethylboron (completely dissociated above 25°) being much less stable than trimethylamine–trimethylboron (K_{100}, 0·472 atm.) while quinuclidine–trimethylboron (K_{100}, 0·0196 atm.) is more stable.[9]

It appears likely that similar steric effects control the dimerisation and thus provide an explanation for the striking difference in behaviour of the two groups of *sec.*-aminoboron dihalides. The small steric requirements of the substituents on the nitrogen atoms in dimethylamino-, 1-pyrrolidinyl-, piperidino-, and morpholino-boron dichloride permit intermolecular co-ordinate bond formation and, consequently, cyclisation. The rather larger steric requirements of the substituents in the products obtained from diethyl-, di-*n*-propyl-, and di-*n*-butyl-amine, and 2-methylpiperidine do not allow cyclisation to take place.

The dimerisation of the *sec.*-aminoboron dibromides appears to be subject to the same steric restrictions. The much slower dimerisation observed for these compounds as compared with their chlorine analogues may be attributed to the increased steric requirements of the boron dibromide group. The much more rapid formation and greater stability of the dimer from 1-pyrrolidinylboron dibromide as compared with the dimer from the piperidino-compound are no doubt due to the lower steric effects of the α-methylene groups in the five-membered pyrrolidine ring.[8]

[8] H. C. Brown and Gerstein, *J. Amer. Chem. Soc.*, 1950, **72**, 2926.
[9] H. C. Brown and Sujishi, *ibid.*, 1948, **70**, 2878.

Experimental

Analyses were by the Microanalytical Section of this Department.

Monomeric sec.-*Aminoboron Dihalides.*—A solution of the secondary amine (0·2 mol.) in dry benzene (50 ml.) was added during ½ hr. to a stirred solution of the boron trihalide (0·2 mol.) in the same solvent (50 ml.) at 0°. Moisture was carefully excluded. To the resulting crystalline suspension or solution of the amine–boron trihalide addition compound was added, in a similar manner, a solution of triethylamine (0·2 mol.) in dry benzene (75 ml.). The mixture was stirred at room temperature for ½ hr., kept overnight to ensure complete separation of the triethylammonium halide, and filtered. The filtrate frequently separated into two layers. After removal of the benzene, distillation of the residue under reduced pressure gave the monomeric *aminoboron dihalide* (Table 1) in 35—50% yield, as a colourless mobile liquid which fumed vigorously in moist air and decomposed violently on contact with water.

Table 1. *Monomeric* sec.-*aminoboron dihalides*, $R_2\overset{+}{N}=\overset{-}{B}X_2$.

R_2	$-[CH_2]_4-$	$-[CH_2]_4-$	$O(CH_2{\cdot}CH_2-)_2$	$-[CH_2]_4-$	$-[CH_2]_5-$
X	Cl	Cl	Cl	Br	Br
B. p./mm.	70—74°/17	82—83°/20	88—90°/25	97—100°/15	105—106°/14

Dimeric sec.-*Aminoboron Dihalides.*—1-Pyrrolidinyl-, piperidino-, and morpholino-boron dichloride began to deposit crystals within a few hours of their isolation and after 1—2 weeks had almost completely solidified. After the solids had been washed with benzene to remove small amounts of dark oils and any monomeric material, the *dimers* were obtained as colourless, highly crystalline solids which did not require further purification. The dimerisation of piperidinoboron dichloride also occurred when a solution of the monomer in benzene was kept for one month at room temperature; the dimer crystallised from the solution in large colourless prisms. The dimerisation of 1-pyrrolidinyl- and piperidino-boron dibromide was effected by heating the

Table 2. *Dimeric* sec.-*aminoboron dihalides*, $(R_2\overset{+}{N}{\cdot}\overset{-}{B}X_2)_2$.

R_2		$-[CH_2]_4-$	$-[CH_2]_5-$	$O(CH_2{\cdot}CH_2-)_2$	$-[CH_2]_4-$	$-[CH_2]_5-$
X		Cl	Cl	Cl	Br	Br
M. p.		131—132°	105°	103°	157—158°	130·5—131·5°
Formula		$C_8H_{16}N_2B_2Cl_4$	$C_{10}H_{20}N_2B_2Cl_4$	$C_8H_{16}O_2N_2B_2Cl_4$	$C_8H_{16}N_2B_2Br_4$	$C_{10}H_{20}N_2B_2Br_4$
Found (%)	C	32·15	36·6	28·55	19·85	24·05
	H	5·4	6·2	4·75	3·3	4·0
	N	9·3	8·55	8·15	5·6	4·35 ‡
	Br	—	—	—	66·25	62·65
	Cl	46·45	42·95	42·0	—	—
Found	*M* *	313	336	288	475	315 †
Required (%)	C	31·65	36·2	28·65	19·95	23·55
	H	5·3	6·1	4·8	3·35	3·95
	N	9·2	8·45	8·35	5·8	5·5
	Br	—	—	—	66·4	62·75
	Cl	46·7	42·75	42·25	—	—
Required	*M* *	303·7	331·8	335·7	481·5	509·55

* Determined ebullioscopically in benzene (concn. 10—20 mg./20 ml.).
† Initial value *ca.* 490. ‡ The reason for this low value is unknown.

compounds at 80° for 7 days and then keeping them at room temperature. After 9 days the 1-pyrrolidinyl compound had completely solidified; the piperidino-compound had not dimerised completely after 9 months. In both cases the *dimers* were obtained as colourless crystalline solids after washing with benzene. The m. p.s and analyses are recorded in Table 2.

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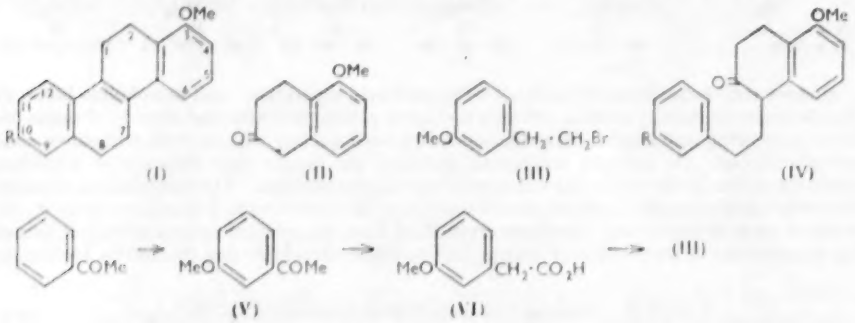
830. *The Synthesis of* 1 : 2 : 7 : 8-*Tetrahydro*-3-*methoxy- and* 1 : 2 : 7 : 8-*Tetrahydro*-3 : 10-*dimethoxy-chrysene.*

By J. F. Collins and Herchel Smith.

The synthesis of the hydrochrysenes of the title is described. Light-absorption data for these and the corresponding chrysenes are recorded. A convenient route to *m*-methoxyphenethyl bromide from acetophenone is demonstrated.

In connection with the synthesis of (±)-18 : 19-bisnor-D-homosteroids,[1] we required an efficient preparation of the previously unknown 1 : 2 : 7 : 8-tetrahydro-3 : 10-dimethoxychrysene (I; R = OMe). The route selected involved alkylation of the readily available [2] 5-methoxy-2-tetralone (II) with *m*-methoxyphenethyl bromide (III) and cyclodehydration of the intermediate (IV; R = OMe) to the chrysene derivative (I; R = OMe).



As a model we treated the sodium derivative of the tetralone (II) with phenethyl bromide in *iso*propyl alcohol and obtained the ketone (IV; R = H) in 33% yield. This was improved somewhat by substituting phenethyl iodide for the bromide and carrying out the reaction in benzene. Cyclodehydration with polyphosphoric acid at 180° furnished the tetrahydrochrysene (I; R = H) which was dehydrogenated with sulphur at 230° to 3-methoxychrysene m. p. 188—190°. Cook and Schoental [3] gave m. p. 167—168°. Our specimen, purified by chromatography on alumina, had light absorption characteristics similar to those determined [4] for Cook and Schoental's compound.

For synthesis of the methoxy-analogue (I; R = OMe) an adequate supply of *m*-methoxyphenethyl bromide was necessary. This compound had previously been prepared in quantity from *m*-hydroxybenzaldehyde [5] or *m*-bromo- [6] or *m*-iodo-aniline,[7] all expensive starting materials. We have now devised what is at least as efficient a synthesis from the much cheaper acetophenone. By published procedures, the latter was converted through the *m*-nitro-, *m*-amino- and *m*-hydroxy-derivatives into *m*-methoxyacetophenone (V) in an overall yield of 50%. The Willgerodt reaction (Kindler modification) [8] then gave *m*-methoxyphenylacetic acid (VI), which was transformed by lithium aluminium hydride into *m*-methoxyphenethyl alcohol and thence by phosphorus tribromide into the bromide (III). This with the potassium derivative of the tetralone (II) in benzene gave >80% yields of product (IV; R = OMe), cyclodehydration of which with polyphosphoric acid at 70° gave the desired tetrahydrochrysene (I; R = OMe) [*ca.* 50% from (III)]. The

[1] Birch and Smith, unpublished work.
[2] Cornforth and Robinson, *J.*, 1949, 1855.
[3] Cook and Schoental, *J.*, 1945, 288.
[4] Holiday and Jope, *Spectrochim. Acta*, 1950, **4**, 157.
[5] Rapson and Robinson, *J.*, 1935, 1533.
[6] Silverman and Bogert, *J. Org. Chem.*, 1946, **11**, 34.
[7] Bachmann and Thomas, *J. Amer. Chem. Soc.*, 1942, **64**, 94.
[8] Schwenck and Bloch, *ibid.*, p. 3051.

light-absorption properties of the products (IV; R = H and OMe), the corresponding chrysenes, and 4 : 10-dimethoxychrysene are recorded below.

Experimental

Evaporations were carried out under reduced pressure. Light petroleum without further definition means the fraction of b. p. 60—80°. Absorption spectra were determined by Mr. F. Hastings and Mrs. L. Skatterböl under the supervision of Dr. F. B. Strauss. Ultraviolet absorption spectra in EtOH were determined with a Unicam SP-500 spectrophotometer; those in hexane were determined with a Beckman DU spectrophotometer modified by Mr. A. E. Thompson of this department to a single-beam automatically recording instrument.

5-Methoxy-1-phenethyl-2-tetralone (IV; R = H).—(*a*) 5-Methoxy-2-tetralone [8] (10 g.) in *iso*propyl alcohol was added with stirring to a solution of sodium *iso*propoxide (from the metal, 1·3 g.) in *iso*propyl alcohol (50 c.c.) under nitrogen. Phenethyl bromide (10·7 g.) was added and the mixture refluxed with stirring for 12 hr. After cooling, hydrochloric acid (10 c.c.) was added and the mixture extracted with ether. The ether solution was washed with water, dried (Na_2SO_4), and evaporated to an oil which was shaken with saturated aqueous sodium hydrogen sulphite (50 c.c.) for 30 min. The solid was collected and washed thoroughly with ether, and the washings were combined with the ether extract of the filtrate. The ether solution was dried and evaporated. Distillation of the residue gave *5-methoxy-1-phenethyl-2-tetralone* as a yellow viscous oil (5·3 g., 33%), b. p. 168—174°/0·05 mm. (Found: C, 81·5; H, 7·4. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·1%). Use of phenethyl iodide and a reaction time of 6 hr. raised the yield to 44%. The 2 : 4-*dinitrophenylhydrazone* was obtained from ethyl acetate as yellow needles, m. p. 137° (Found: N, 11·9. $C_{25}H_{24}O_5N_4$ requires N, 12·2%).

(*b*) 5-Methoxy-2-tetralone (8 g.) in benzene (50 c.c.) was added to finely powdered sodium (1·12 g.) in benzene (50 c.c.) under nitrogen, and the solution refluxed with stirring for 1 hr., then phenethyl iodide (10 g.) in benzene (30 c.c.) was added. Refluxing was continued for a further 5 hr. After cooling, the mixture was acidified with 2N-sulphuric acid, and the benzene layer was separated and combined with the benzene extract of the aqueous layer. The benzene solution was washed with water, dried, and evaporated to an oil, distillation of which gave the tetralone (IV; R = H) (4·8 g.), b. p. 180—185°/0·08 mm.

1 : 2 : 7 : 8-*Tetrahydro-3-methoxychrysene* (I; R = H).—The 2-tetralone (IV; R = H) (2 g.) was added with stirring to a solution of phosphoric anhydride (9 g.) in phosphoric acid (*d* 1·75; 9 c.c.) at 120° under nitrogen. The mixture was then heated at 180° for 45 min., cooled to 90°, and poured into water. The product was collected with ether, and the ether solution was washed with aqueous sodium hydroxide and water, dried (Na_2SO_4), and evaporated. The residual oil (1·3 g.) was taken up in carbon tetrachloride and adsorbed on activated alumina. Elution with carbon tetrachloride gave 1 : 2 : 7 : 8-*tetrahydro-3-methoxychrysene*, obtained from light petroleum (b. p. 40—60°) as needles (0·9 g., 51%), m. p. 80° (Found: C, 87·1; H, 7·0. $C_{19}H_{18}O$ requires C, 87·0; H, 6·9%). Light absorption: (*a*) in EtOH, $\lambda_{max.}$ 230, 256, 266, 274 (infl.), 299 (infl.), 310, 324, and 340 mμ ($10^{-3}\varepsilon$ 20·7, 7·9, 9·8, 7·0, 13·6, 19·9, 23·1, and 15·6); (*b*) in hexane, $\lambda_{max.}$ 232·2, 238·4 (infl.), 256, 266, 274 (infl.), 299 (infl.), 312, 325, and 340·5 mμ ($10^{-3}\varepsilon$ 22·1, 19·5, 15·0, 8·3, 11·3, 8·0, 15·0, 22·3, 26·1, and 16·8).

The *trinitrobenzene complex* separated from ethanol as orange needles, m. p. 177—178° (decomp.) (Found: C, 53·7; H, 3·6; N, 11·7. $C_{19}H_{18}O,2C_6H_3O_6N_3$ requires C, 54·1; H, 3·5; N, 12·2%).

3-*Methoxychrysene.*—1 : 2 : 7 : 8-Tetrahydro-3-methoxychrysene (400 mg.) was heated with sulphur (115 mg.) at 180—230° during 2 hr. On cooling, the solid was extracted with benzene–light petroleum (1 : 1), and the solution evaporated to a crystalline residue (390 mg.), m. p. 184—186°, which was purified by percolating its solution in benzene through a column of activated alumina (5 g.). Recrystallisation from benzene–light petroleum (1 : 1) (Norit) gave 3-methoxychrysene as plates, m. p. 188—190° (Cook and Schoental give m. p. 167—168°) (Found: C, 88·2; H, 5·3. Calc. for $C_{19}H_{14}O$: C, 88·4; H, 5·4%). Light absorption: (*a*) in EtOH, $\lambda_{max.}$ 229, 262, 270, 292, 305, 315, 327·5, 347, and 365 mμ ($10^{-3}\varepsilon$ 31·5, 63·3, 72·4, 8·5, 13·2, 10·4, 10·1, 3·0, and 1·8); (*b*) in hexane, $\lambda_{max.}$ 229·6, 261, 270, 292, 304·5, 317, 330, 345, and 362 mμ ($10^{-3}\varepsilon$ 31·5, 60·5, 69·8, 8·5, 14·0, 11·8, 10·4, 2·9, and 2·9). Holiday and Jope [4] give for hexane solutions: $\lambda_{max.}$ 270·5, 291·2, 303·5, 316·9, 328·7, 345·6, and 363·2 mμ ($10^{-3}\varepsilon$ 106, 10·0, 15·9, 13·8, 11·6, 2·9, and 3·1).

m-*Methoxyacetophenone.*—*m*-Nitroacetophenone, prepared by Cobb's method,[10] was reduced

[9] Birch and Smith, *J.*, 1951, 1882.
[10] Cobb, *Proc. South Dakota Acad. Sci.*, 1945, **23**, 64; *Chem. Abs.*, 1946, **40**, 7180.

with iron filings and dilute acetic acid to *m*-aminoacetophenone [11] which was converted into *m*-hydroxyacetophenone by a conventional diazotisation procedure.[12] The crude *m*-hydroxyacetophenone was methylated directly with 30% aqueous potassium hydroxide and methyl sulphate in methanol, and the product was purified by steam-distillation and fractionation to give *m*-methoxyacetophenone, b. p. 125°/14 mm. (73% from *m*-aminoacetophenone; *ca.* 50% from acetophenone).

m-*Methoxyphenethyl Bromide*.—*m*-Methoxyacetophenone (50 g.), sulphur (16 g.), and morpholine (36 g.) were refluxed for 8 hr. Sodium hydroxide (42 g.) in ethanol (420 c.c.) was added and the solution was refluxed for a further 15 hr. The alcohol was distilled off and the residue acidified with hydrochloric acid (ice-cooling). The precipitate was collected and recrystallised from water, to give *m*-methoxyphenylacetic acid as plates (27·8 g.), m. p. 65° (lit.,[13] m. p. 68°). A further crop (5·5 g.) was obtained by concentrating the mother-liquors. The foregoing acid was reduced with lithium aluminium hydride to *m*-methoxyphenethyl alcohol,[14] which was converted by Bachmann and Thomas's method [7] into *m*-methoxyphenethyl bromide b. p. 135—138°/9 mm. (35—38% from *m*-methoxyacetophenone).

5-Methoxy-1-m-methoxyphenethyl-2-tetralone (IV; R = OMe).—5-Methoxy-2-tetralone (8·9 g.) in benzene (40 c.c.) was added with stirring to finely powdered potassium (1·97 g.) in benzene (80 c.c.) under nitrogen, and the mixture was refluxed for 1·5 hr., whereafter *m*-methoxyphenethyl bromide (9·9 g.) in benzene (25 c.c.) was added. The stirring and refluxing were continued for a further 21 hr., and a little methanol was added to the cooled mixture to decompose any unchanged potassium. 2N-Sulphuric acid (40 c.c.) was added and the mixture was extracted with ether (4 × 10 c.c.). The combined extracts were washed with water, dried, and evaporated. Distillation of the residual oil gave *5-methoxy-1-m-methoxyphenethyl-2-tetralone* (10·9 g., 81%), b. p. 208°/0·05 mm. A sample was redistilled for analysis (Found: C, 77·4; H, 7·1. $C_{20}H_{22}O_3$ required C, 77·4; H, 7·1%).

1 : 2 : 7 : 8-Tetrahydro-3 : 10-dimethoxychrysene (I; R = OMe).—A solution of phosphoric anhydride (32·7 g.) in phosphoric acid (*d* 1·75; 49 c.c.) at 75° was rapidly added with stirring to the foregoing 2-tetralone (IV; R = OMe) (10·9 g.) at the same temperature under nitrogen. The temperature was maintained at 75—80° for 20 min. The cooled mixture was decomposed with ice and thoroughly extracted with ethyl acetate–ether (1 : 1). The extract was washed with water, dried, and evaporated to a gum which was dissolved in warm ether (50 c.c.) from which the *1 : 2 : 7 : 8-tetrahydro-3 : 10-dimethoxychrysene* separated as needles (5·86 g.), m. p. 119—120°. The residual gum from the mother-liquors was taken up in benzene (30 c.c.) and adsorbed on alumina (75 g.). Elution with benzene–light petroleum (1 : 1) gave a further crop (0·75 g.), m. p. 121—122°. A portion recrystallised for analysis had m. p. 122—123° (Found: C, 81·9; H, 7·1. $C_{20}H_{20}O_2$ requires C, 82·2; H, 6·9%). Light absorption in EtOH: $\lambda_{max.}$ 230, 267, 315, 330, and 345 mμ ($10^{-3}\varepsilon$ 15·1, 4·4, 19·0, 21·4, and 15·0). The *trinitrobenzene complex* was obtained from ethanol as red needles, m. p. 162° (decomp.) (Found: C, 53·6; H, 3·8; N, 11·7. $C_{20}H_{20}O_2,2C_6H_3O_6N_3$ requires C, 53·4; H, 3·6; N, 11·8%).

3 : 10-Dimethoxychrysene.—*1 : 2 : 7 : 8-Tetrahydro-3 : 10-dimethoxychrysene* (400 mg.) was heated with 30% palladised charcoal (80 mg.) at 250° for 10 min. The temperature was raised to 300° during 2 hr. The cooled mixture was extracted with benzene (5 × 25 c.c.), and the solution concentrated to 5 c.c. and percolated through alumina (5 g.). The product was thrice recrystallised from benzene–light petroleum, to give *3 : 10-dimethoxychrysene* (120 mg.), m. p. 200° (Found: C, 83·1; H, 5·5. Calc. for $C_{20}H_{16}O_2$: C, 83·3; H, 5·5%). Johnson and his co-workers [15] give m. p. 198·5—200°. Light absorption: (*a*) in EtOH, $\lambda_{max.}$ 231, 262, 274, 310, 327, 350, and 365 mμ ($10^{-3}\varepsilon$ 26·0, 62·5, 85·0, 16·7, 9·4, 2·2, and 1·8); (*b*) in hexane, $\lambda_{max.}$ 231·8, 261·9, 274·9, 308, 327, 348, and 364 mμ ($10^{-3}\varepsilon$ 25·9, 57·6, 75·3, 17·0, 10·1, 3·2, and 2·3). Light absorption of *4 : 10-dimethoxychrysene* [8] in EtOH: $\lambda_{max.}$ 255, 265, 275, 296, 306, and 317 mμ ($10^{-3}\varepsilon$ 33·0, 64·3, 125·1, 19·1, 15·4, and 7·7).

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Dyson Perrins Laboratory, Oxford. [*Received, June 15th*, 1956.]

[11] Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 653.
[12] Cf. Icke, Redemann, and Burnett, *Org. Synth.*, 1949, **29**, 63.
[13] Chakravarti, Haworth, and Perkin, *J.*, 1927, 2265.
[14] Hunter and Hogg, *J. Amer. Chem. Soc.*, 1949, **71**, 1918.
[15] Johnson, Banerjee, Schneider, Gutsche, Shelberg, and Chinn, *J. Amer. Chem. Soc.*, 1952, **74**, 2832.

831. *Ionophoresis of Carbohydrates. Part IV.* Separations of Carbohydrates on Fibreglass Sheets.*

By E. J. Bourne, A. B. Foster, and P. M. Grant.

The behaviour of fibreglass sheets as electrolyte supports during ionophoresis of carbohydrates in borate buffer has been examined. The main advantages of the use of fibreglass, rather than filter-paper, are that non-reducing carbohydrates are much more easily detected, that the absorption of amylosaccharides is considerably reduced, and that the greater electro-endosmotic flow facilitates separations of sugars with similar absolute mobilities. There are only slight differences between the M_G values on fibreglass and on filter-paper.

The separation of carbohydrates as their borate complexes by zone electrophoresis (ionophoresis) on paper strips, with the enclosed-strip technique,[1] has been well studied,[2] and recently the ionophoretic behaviour, on paper, of the *N*-benzylglycosylamines has been described.[3] There are some disadvantages in the use of paper strips as electrolyte supports, *e.g.*, numerous non-reducing carbohydrates and polysaccharides are difficult to locate after migration and certain polysaccharides, especially amylosaccharides, tend to be adsorbed.[2] Recently a fibreglass sheet of suitable structure has become available commercially and we report herein its behaviour, in comparison with that of paper (Whatman No. 3), as an electrolyte support in the ionophoresis of carbohydrates.

The fibreglass sheets had capillary properties similar to those of paper but, when borate-soaked, had a lower electrical resistance. D-Glucose had a lower absolute mobility on paper ($3{\cdot}66 \times 10^{-6}$ cm.^{2} v^{-1} sec.$^{-1}$) than on fibreglass ($4{\cdot}92 \times 10^{-6}$ cm.^{2} v^{-1} sec.$^{-1}$) (Table 2), as did all the other carbohydrates listed in Table 1. However, the relative mobilities, as expressed by the M_G values,[2] showed only slight differences in the two cases (Table 1); for

TABLE 1. *Comparative M_G values (error $\pm 0{\cdot}02$) on paper and fibreglass strips.*

Substance	M_G value: Paper	Fibreglass	Substance	M_G value: Paper	Fibreglass
DL-Glyceraldehyde	0·79	0·75	Maltose	0·34	0·30
1 : 3-Dihydroxyacetone	0·78	0·75	Gentiobiose	0·72	0·69
L-Arabinose	0·96	0·94	Glycerol	0·44	0·39
D-Ribose	0·77	0·74	*meso*Erythritol	0·75	0·70
D-Xylose	1·00	1·00	D-Arabitol	0·90	0·86
2-Deoxy-D-ribose	0·33	0·28	D-Glucitol	0·89	0·82
L-Fucose	0·89	0·88	Galactitol	0·98	0·95
L-Rhamnose	0·52	0·49	D-Mannitol	0·90	0·85
D-Galactose	0·93	0·91	D-*glycero*-D-*gala*Heptitol	1·00	0·95
D-Glucose	1·00	1·00	D-*glycero*-D-*manno*Heptitol	0·92	0·87
D-Mannose	0·72	0·67	αα-Trehalose	0·19	0·16
D-Fructose	0·90	0·88	Sucrose	0·18	0·15
L-Sorbose	0·95	0·95	Raffinose	0·28	0·23
L-Galaheptulose	0·89	0·86	Melezitose	0·22	0·21
D-Mannoheptulose	0·87	0·83	D-Glucose-1 phosphate	1·10	1·10
Sophorose	0·33	0·28	D-Glucuronic acid	1·20	1·23
Nigerose	0·69	0·65	Myoinositol	0·53	0·48
Cellobiose	0·29	0·26			

substances with a lower mobility than that of D-glucose ($M_G < 1{\cdot}00$) the M_G values on fibreglass were 0—0·05 unit lower than on paper. Thus there is negligible selective adsorption of the migrating substances on either electrolyte support. It has been inferred from other results[2] that carbohydrates of low molecular weight are not adsorbed on paper during ionophoresis.

* Part III, *J.*, 1956, 30.

[1] Foster, *Chem. and Ind.*, 1952, 1050; Gross, *Nature*, 1953, **172**, 908.
[2] Foster, Newton-Hearn, and Stacey, *J.*, 1956, 30, and references cited therein.
[3] Barker, Bourne, Grant, and Stacey, *Nature*, 1956, **177**, 1125.

The electroendosmotic flow, as measured by the movement of 2 : 3 : 6-tri-*O*-methyl-D-glucose, was towards the cathode for both paper and fibreglass when borate buffer (pH 10) was the electrolyte, but it was exceptionally high with the fibreglass (Table 3). Thus on fibreglass it was necessary to locate the origin line near the anode—on paper it is usually placed near the cathode for neutral carbohydrates. Use can be made of the high electroendosmotic flow with fibreglass in separations of carbohydrates which have M_G values similar to that of D-glucose. On fibreglass the migration of D-glucose is strongly opposed by the electroendosmotic flow (Table 3), so that the apparent migration distance is low. Thus the effective length of the fibreglass strip is increased, *e.g.*, a separation of D-glucose and D-galactose which on paper requires an apparent migration distance of *ca.* 40 cm. can be achieved on fibreglass in *ca.* 10 cm. In theory the separation on fibreglass can be improved by continuing the ionophoresis for a much longer period, but unfortunately the spots tend to become more diffuse on fibreglass than on paper; however, diffusion effects may be reduced appreciably [4] by operating at very high voltage gradients, though then very efficient cooling is essential.

Because of its chemical inertness, the detection of carbohydrates on fibreglass is much easier than on paper. Reducing sugars can easily be located on either support. With non-reducing carbohydrates, much more drastic staining procedures can be applied to fibreglass (see Experimental section).

The ionophoretic behaviour of amylose on paper in the presence of borate has already been described.[2] The polysaccharide was strongly adsorbed; the pattern of migration depended on the amount of amylose introduced on the paper and on the manner in which it was introduced. Amylose was selected for ionophoretic study on fibreglass because it is the most strongly adsorbed, on cellulose, of all the polysaccharides so far examined. A large migration towards the cathode, with very weak adsorption in the path of movement and negligible adsorption at the origin, occurred when a solution of amylose in borate buffer, but not when an aqueous solution, was put on fibreglass and ionophoresis in borate buffer was subsequently performed. However, the M_G value (0·21) indicated a significant movement against the electroendosmotic flow towards the anode (cf. M_G 0·18 on paper [2]). It appears that there is considerably less adsorption of amylose on fibreglass than on paper under optimum conditions. Amylose was detected on fibreglass by means of iodine or ammoniacal silver nitrate. Although the sensitivity of the latter reagent was not examined in detail, it clearly revealed the small traces of amylose (as indicated by the iodine method of known high sensitivity [2]) left in the path of migration of the main zone. Ammoniacal silver nitrate is of potential value for the detection, on fibreglass, of polysaccharides which do not react with iodine. Attempts to detect amylose and other polysaccharides on paper with ammoniacal silver nitrate were mainly unsuccessful.

Amylopectin has an M_G value of 0·31 on fibreglass (cf. 0·25 on paper [2]). The migration pattern obtained on ionophoresis of an artificial mixture of amylose and amylopectin indicated some association and only a partial separation. This behaviour contrasts with that on paper.[2]

The ability of certain sugars to form complexes with aqueous calcium chloride indicated a possible new method for ionophoretic separation of sugars. However, with an aqueous solution of calcium chloride on both filter-paper and fibreglass supports, L-arabinose and D-mannose, which readily form complexes,[5] could not be separated from D-glucose, which does not. Thus it appears that the sugar in such a complex is not part of an ionic species. The ionophoretic behaviour on fibreglass of the *N*-benzylglycosylamines will be described elsewhere.[6]

Experimental

The fibreglass sheets were supplied by H. Reeve Angel and Co. and were used without pretreatment. Whatman No. 3 paper was employed for comparisons. The capillary properties of fibreglass and paper were similar in that equal volumes of liquid gave only slightly larger circular spots on the fibreglass.

[4] Gross, *Nature*, 1955, **176**, 362.
[5] Pigmann and Goepp, "Carbohydrate Chemistry," Academic Press, New York, 1948, p. 48.
[6] Barker, Bourne, Grant, and Stacey, unpublished results.

Ionophoresis.—The apparatus and technique employed have been described elsewhere.[1] Solutions of the migrating substances were introduced on to the smooth side of the fibreglass. The electrolyte was 0·2M-sodium borate (pH 10). For comparisons strips of fibreglass and paper (38 × 10 cm.) were used under a standard potential of 500 v (*i.e.*, *ca.* 15 v/cm. for the effective length of 34 cm.). The results in Table 2 are typical of many.

TABLE 2. *Ionophoresis of* D-*glucose* (1·5 *hours*).

	Final current (milliamps)	Absolute distance (cm.) of migration	Mobility (10^{-5} cm.^{2} v^{-1} sec.$^{-1}$)
Whatman No. 3 paper	15	9·9	3·66
Fibre glass	21	13·2	4·92

Slight variations in the mobilities (and in the M_g values in Table 1) were observed in duplicate experiments for a given system. Elimination of the variations is difficult experimentally since it would demand precise control of (1) the quality and thickness of the paper and fibreglass, (2) the blotting process in the preparation of the paper,[1] (3) the clamping of the glass plates which enclose the paper or fibreglass,[1] (4) the amount of the migrating substances introduced on to the paper, and (5) temperature. The relative positions of the spots on individual "pherograms"[7] was less variable.

The M_g values recorded in Table 1 were determined as previously described,[1,2] 2 : 3 : 6-tri-*O*-methyl-D-glucose being used to determine movement due to electroendosmotic flow, the extent of which is indicated in Table 3. In preparing the paper and fibreglass for ionophoresis 1 drop of a 1·6% aqueous solution of each substance was introduced on to each electrolyte support to give a spot *ca.* 0·4 cm. in diameter. After ionophoresis under the standard conditions the spots on paper had diffused to *ca.* 0·7 cm. in diameter and those on fibreglass to *ca.* 1·0 cm. in diameter.

TABLE 3.

	Observed movement of sugar derivative :*	
	on fibreglass	on paper
D-Glucose	2 cm. ⟶ cathode	8 cm. ⟶ anode
2 : 3 : 6-Tri-*O*-methyl-D-glucose	15 cm. ⟶ cathode	2 cm. ⟶ cathode

* The extent of the electroendosmotic flow must be taken into consideration when selecting the position of the origin line.

Detection of the Migrating Substances.—Detection was carried out as customary for the reagents described, unless otherwise stated.

(a) *Aniline hydrogen phthalate.*[8] Equally effective for reducing sugars on both fibreglass and paper.

(b) *Ethanolic sodium hydroxide–silver nitrate.*[9] This reagent would detect all reducing sugars, and many non-reducing carbohydrates, on both fibreglass and paper in the absence of borate. The sensitivity was reduced appreciably on borate-impregnated fibreglass and paper, *e.g.*, hexitols and pentitols could not be detected. On fibreglass the spots which appeared were black on a pale grey background.

(c) *Ammoniacal silver nitrate.*[10] All reducing and most non-reducing carbohydrates so far examined are detectable by this reagent at 7% strength. The tendency for paper itself to react with the reagent results in considerable background interference in the detection of non-reducing carbohydrates and only one application of the spray is possible. With fibreglass there is negligible background interference and the spray may be applied several times if necessary. Spots appear black on a pale grey background.

(d) *Alkaline permanganate.* By means of water containing 1·0% of potassium permanganate and 2·0% of sodium carbonate reducing and non-reducing carbohydrates showed on fibreglass as yellow spots on a purple background. The background slowly (3 days) became yellow at room temperature under the influence of light and rapidly (20 min.) at 100°. On paper the background became brownish-yellow at room temperature in 10 min. and immediately on heating.

[7] Bücher, Matzelt, and Pette, *Klin. Wochenschr.*, 1952, **30**, 325.
[8] Partridge, *Nature*, 1949, **164**, 443.
[9] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[10] Hough, *Nature*, 1950, **165**, 400.

(e) *Periodate–benzidine.*[11] All the periodate in the reagent reacts when paper alone is sprayed and heated (10 min. at 100°), whereas under similar conditions on fibreglass it is largely unchanged. The migrating zones on fibreglass appear as white spots on a blue background.

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[11] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.

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832. *Electronic Spectra of Organic Molecules and their Interpretation. Part II.* Effect of Terminal Halogen Atoms of Conjugated Systems on K-Bands.†*

By A. BURAWOY and A. R. THOMPSON.

The effect of halogen atoms at the ends of the conjugated systems (1) and (2) on the position of the corresponding *K*-bands is studied,

(1) p-Hal·C_6H_4·B (B = H, $\overset{+}{N}H_3$, CHO, $CH{:}\overset{+}{O}H$, NO_2) ⟶

(2) p-A·C_6H_4·Hal (A = Ph, OMe, O^-, NH_2, I) ⟶

The *K*-bands are displaced to longer wavelengths with increasing polarisability of the C–Hal electrons, *i.e.*, in the order C–F ⟶ C–I (in both directions) and to a smaller degree with increasing polarity (and resulting polarisability) of the absorbing system in the direction of the "effective" electronic migration of the transition. The polarisability of the C–F electrons towards the fluorine atom is appreciably smaller than that of the C–H electrons towards hydrogen, resulting in a blue-shift of the *K*-bands in system (2). A comparison of the *K*-bands of the *p*-halogenobenzaldehydes and their conjugate acids indicates that with increasing electron demand by the carbon atom the electron shift in the ground state increases in the order C–F ⟶ C–I. The reported observations cannot be explained with the help of structures involving non-localised bonds, and mesomeric (electromeric) electron displacements, and by consideration of π electrons only, but are consistently accounted for by inductomeric electron displacements in systems built up of localised bonds only.

AN investigation of the effect of terminal methyl and substituted methyl groups (A or B) of conjugated systems (I) on the position of the corresponding *K*-bands [1] has reaffirmed that the observations related to the electronic spectra of organic compounds cannot be accounted for by the widely accepted theoretical interpretations based on molecular structures involving non-localised bonds (many-centred orbitals) and on the simplifying assumption that only the π electrons are important or need to be considered for the electronic transitions. However, they can be understood with the help of classical structures involving only localised bonds and inductive electron displacements.[2,3]

On this basis, an absorbing (conjugated) system (such as I) can be considered as a system of interacting smaller polarisable units (electron pairs or even the single electrons). The electron migration along the absorbing system which corresponds to the transition responsible for a *K*-band is facilitated by an increase in the polarity of the individual bonds

* Part I, *J.*, 1955, 2557.
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Burawoy and Spinner, *J.*, 1955, 2557.
[2] Burawoy, *Trans. Faraday Soc.*, 1944, **40**, 537; *Discuss. Faraday Soc.*, 1951, **10**, 104; *Chem. and Ind.*, 1944, 434; "Contribution to the Study of Molecular Structure," Desoer, Liège, 1947—1948, p. 73.
[3] Burawoy and Spinner, *J.*, 1954, 5438.

or by their replacement by other more strongly polarisable units. This will stabilise the excited state and cause a red-shift of the *K*-band. Thus, the effect of any terminal atom or group (I; A or B) will be due mainly to two factors, the degree of the polarisability of its electron system and the change of the polarity of the substituted system.

(I) A·[CH=CH]$_n$·B

Experimental evidence has also been given [1] that the " effective " electron migration in one direction along the absorbing system determines the stability of the excited state, *i.e.*, that in qualitative comparative discussions of electronic spectra the accompanying (complementary) electron migration in the opposite direction can generally be neglected (cf., however, below). In the present paper, the discussion is extended to the effect of terminal halogen atoms (I; A or B = F, Cl, Br, I) on the position of the corresponding *K*-bands.

The polarity of the C–Hal bonds in alkyl halides is known to increase in the order C–I $\ll$ C–Br $<$ C–Cl $\ll$ C–F. It is reduced in the halogenoethylenes, halogenobenzenes, and other systems, in which the halogen atom is attached to a carbon atom participating in a multiple linkage. As already shown,[2,3] this involves inductive electron displacements (accompanied by changes of the interatomic distances) resulting from the increased effective nuclear charge (electron deficiency) at such carbon atoms, rather than a delocalisation of the unshared electrons of the halogen atoms (mesomeric effect). The greater acidity of the halogenobenzoic acids and halogenophenylacetic acids than of the parent acids [4] shows that the halogen atoms in these compounds are still electron attracting. There is no reason to suppose that in other comparable series the polarity of the C–Hal bonds is reversed or that, as the electron demand by the carbon atom increases, the normal order of the C–Hal polarities becomes inverted, *i.e.*, that the reduction of the polarity increases in the order C–I $<$ C–Br $<$ C–Cl $<$ C–F.

Observations such as the smaller acidity of *p*-fluorophenol ($10^{10}K$, 0·26) than of phenol (0·32) or the increasing acidity of the *p*-halogenophenols in the order F (0·26) $<$ Cl (1·32) $<$ Br (1·55) $<$ I (2·19) [4] do not represent such evidence. Equilibria or rates of chemical reactions are determined not only by the polar effects of the halogen atoms (or other substituents), but also, often decisively, by the differences of the C–Hal bond energies in the two entities involved, *i.e.*, the stabilisation energies and bond contractions resulting from an increased electron demand.[2,3] These observations show conclusively only that the stabilisation energies increase in the order C–I $<$ C–Br $<$ C–Cl $<$ C–F, but do not give information about the accompanying relative changes of the bond polarities. It has been one aim of the present investigation to elucidate this matter.

We have determined the electronic spectra in ethanol and in hexane of the halogenobenzenes, of diphenyl, anisole, aniline, iodobenzene, nitrobenzene, benzaldehyde and their *p*-halogeno-derivatives, in 99% ethanol of the *p*-halogenoanilinium ions, and in ethanol and water of the *p*-halogenophenoxide ions, and the spectra of the conjugate acids of the benzaldehydes in concentrated sulphuric acid. Data for the positions and molecular extinction coefficients of the maxima of the *K*-bands as well as the displacements in Å units caused by the halogen atoms are shown in Table 1. Our determinations were carried out with a Hilger E3 quartz spectrograph fitted with a Spekker photometer, but most data have also been confirmed with a Hilger Uvispek photoelectric spectrophotometer. The reported data below 2190 Å have been obtained by the latter method. The experimental error is not more than 5 Å in the position of the maxima and 10% in the molecular extinction coefficient. The order of the differences (sometimes only small) between the parent substances and the fluoro-derivatives on the one hand and of the chloro- and bromo-derivatives on the other is certain. The position of the *K*-band of benzene has been taken to be 2030 Å in ethanol and 2020 Å in hexane, 2035 Å in water and 2020 Å in heptane being reported by Doub and Vandenbelt [5] and by Platt and Klevens,[6] respectively.

Halogenobenzenes.—The *K*-band of benzene is displaced to longer wavelengths in the

[4] Dippy, *Chem. Reviews*, 1939, **35**, 151.
[5] Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714.
[6] Klevens and Platt, Tech. Rept. 1953—1954, Part I, Office of Naval Research.

TABLE 1. *Maxima (in Å) of K-bands of* p-R·C_6H_4·X.

R	X =	Solv.		H	F	Cl	Br	I
H		EtOH [a]	λ	~2030	2068	2130 [b]	2135 [b]	2275 [b]
			ε	—	3000	6100	7300	12,000
			D	—	+38	+100	+105	+245
		C_6H_{14} [c]	λ	~2020	2068	2152	2160	2360 [b,d]
			ε	6600	3000	7600	7700	11,500
			D	—	+48	+132	+140	+280
NH_3^+		EtOH–HCl (99 : 1)	λ	—	2078	2167	2190	2324
			ε	—	3400	8000	8400	12,500
Ph		EtOH	λ	2475	2462	2550	2562	2586
			ε	19,500	18,600	23,500	25,500	25,500
			D	—	−13	+75	+87	+111
		C_6H_{14}	λ	2467	2450	2527	2540	2573
			ε	19,000	16,000	20,500	22,000	22,000
			D	—	−17	+60	+73	+106
I		EtOH	λ	2275	2258	2359	2374	2416
			ε	12,000	10,500	17,000	17,500	18,500
			D	—	−17	+84	+99	+141
		C_6H_{14}	λ	2300 [b]	2262	2363	2390 [b]	2425
			ε	11,000	10,500	16,000	16,500	17,500
			D	—	−38	+63	+90	+125
NH_2 [e]		EtOH	λ	2344	2334	2445	2452	2502
			ε	8000	7000	12,500	13,500	18,500
			D	—	−10	+101	+108	+158
		C_6H_{14}	λ	2340	2305	2414	2418	2463
			ε	7500	7000	12,500	13,000	17,500
			D	—	−35	+73	+78	+123
MeO		EtOH	λ	2195 [f]	2170	2282	2274	2335
			ε	7500	6800	11,500	12,000	16,000
			D	—	−25	+87	+79	+140
		C_6H_{14}	λ	2198 [f]	2163	2280	2270	2339
			ε	7000	5700	11,000	11,500	15,500
			D	—	−35	+82	+72	+141
O^-		0·1% NaOEt in EtOH	λ	2374	2350	2465	2454	2500
			ε	12,500	7500	12,500	17,000	19,000
			D	—	−24	+91	+80	+126
		0·1N-NaOH	λ	2345	2318	2446	2440	2473
			ε	11,000	6000	11,000	11,500	16,000
			D	—	−27	+101	+95	+128
NO_2		EtOH	λ	2595	2622	2699	2755	2940
			ε	9500	9000	11,000	11,500	12,500
			D	—	+27	+104	+160	+345
		C_6H_{14} [g]	λ	2513	2569	2652	2697	2865
			ε	9000	8200	11,000	11,500	12,500
			D	—	+56	+139	+184	+352
CHO		EtOH	λ	2445	2461	2544	2591	2708
			ε	13,000	11,500	16,000	16,500	13,500
			D	—	+16	+99	+146	+263
		C_6H_{14}	λ	2408	2439	2529	2575	2695
			ε	14,000	13,000	17,500	18,500	15,500
			D	—	+31	+121	+167	+287
CH_2OH^+		H_2SO_4	λ	2950	2990	3195	3327	3718
			ε	26,000	23,000	30,000	27,500	21,500
			D	—	+40	+245	+377	+768

[a] Centre of broad band indicating fine structure.

[b] Bowden and Braude (*J.*, 1952, 1068) give 2040, 2100, 2100, and 2260 Å, respectively, for the halogenobenzenes. [c] Ungnade (ref. 7) gives 227 mμ in *cyclo*hexane. [d] Klevens and Platt (ref. 6) give 2146, 2150, and 2278 Å (1st band) for heptane solutions of chloro-, bromo-, and iodo-benzene, respectively. [e] Ungnade (*loc. cit.*) gives 2286 and 2335 Å in *cyclo*hexane. [f] Doub and Vandenbelt (ref. 5) give 230, 239, and 239·5 mμ for aqueous solutions of aniline and *p*-chloro- and *p*-bromo-aniline, respectively. [g] Ungnade (*loc. cit.*) gives 220 and 222 mμ in ethanol and *cyclo*hexane, respectively. [h] Conrad-Billroth, Förster, and Wagner (*Z. phys. Chem.*, 1937, *B*, **35**, 343) give 2560, 2646, and 2680 Å for *p*-fluoro-, *p*-chloro-, and *p*-bromo-nitrobenzene, respectively. Ungnade (*J. Amer. Chem. Soc.*, 1954, **76**, 160) gives spectra of the *p*-halogenonitrobenzenes in 95% ethanol, and Ferguson and Iredale (*J.*, 1953, 2959) those of *p*-fluoro-, -chloro-, and -bromo-iodobenzene in light petroleum.

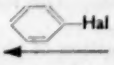
order of substituents, F (*D*, 48 and 38 Å, in hexane and ethanol, respectively) < Cl (*D*, 132 and 100 Å) < Br (*D*, 140 and 105 Å) < I (*D*, 280 and 245 Å). The direction of the effective electron migration of the transition in the halogenobenzenes is towards the phenyl group (II). This follows unambiguously (i) from the displacement of their *K*-bands in ethanol to longer wavelengths (10, 37, 55, 49 Å) in the corresponding *p*-halogenoanilinium ions (see Table 1), the effective electron migration being facilitated by the electron shift (in the ground state) in its direction on introduction of the electron-attracting ammonium group, and (ii) from the displacement of the *K*-bands to shorter wavelengths on replacing hexane by ethanol which is responsible for an electron shift in the opposite direction.

The electron shift in the phenyl group due to the electron-attracting terminal halogen atoms reduces its polarisability, but this effect is masked by the considerably greater polarisability of the C–Hal electrons towards the carbon atom (increasing in the order C–F < C–Cl < C–Br < C–I). The greater electron polarisability [1] of the aliphatic C–Hal system towards the halogen atom than in the opposite direction is reversed as a result of the reduction of the polarity in the aromatic C–Hal bonds (including the shift of the unshared electrons). Whilst the electronic polarisability, being mainly a function of the ionisation potentials and electron affinities of the atoms of a bond, should, in principle, be expected to be greater towards the negative end of the dipole, in the aromatic C–Hal systems (which are treated as a unit) this effect is masked by the contribution of the greater polarisability of the unshared electrons in the opposite direction.

TABLE 2. *Differences (in* Å*) in the position of* K*-bands of* p-R·C_6H_4·X *in hexane and ethanol.* (*D*, Observed displacement. *D'*, Displacement attributed to C–Hal system.)

	X =	H	F		Cl		Br		I	
	R	*D*	*D*	*D'*	*D*	*D'*	*D*	*D'*	*D*	*D'*
(i)	H	+10	0	−10	−22	−32	−25	−35	−25	−35
(ii)	Ph	+8	+12	+4	+23	+15	+22	+14	+13	+5
(iii)	I	−25	−4	+21	−4	+21	−16	+ 9	− 9	+16
(iv)	NH_2	+4	+29	+25	+31	+27	+34	+30	+39	+35
(v)	MeO	−3	+7	+10	+2	+5	+4	+7	−4	−1
(vi)	NO_2	+82	+53	−29	+47	−35	+58	−24	+75	−7
(vii)	CHO	+37	+22	−15	+15	−22	+16	−21	+13	−24

p-*Halogeno-derivatives of Diphenyl, Iodobenzene, Aniline, Anisole, and the Phenoxide Ion.* —The effective electron migration of the *K*-band transition in these compounds is determined by the terminal phenyl, iodo, amino, methoxyl, and charged oxygen substituents, respectively, and is directed towards the halogen atom (III).

(II)  (III)

Thus, in contrast to the halogenobenzenes, on replacing hexane by ethanol the electron shift in the ground state facilitates the effective electron migration of the C–Hal electrons resulting in bathochromic displacements of the *K*-bands. Data for these displacements (*D'*) representing the difference between the displacements (*D*) observed for the parent substances and the corresponding halogen derivatives, are shown in Table 2, (ii)—(v). They are mainly due to a change of the polarity of the absorbing molecules in the ground state, but there is no evidence to show whether, in addition to the dielectric properties of the solvent, any stoicheiometric hydrogen-bond formation of the halogen atoms with ethanol makes some contribution, as recently suggested by Ungnade.[7]

The direction of the effective electron migration (as in III) is also supported by an analysis of the effect of the methoxyl, amino, iodo, and charged oxygen substituents in the *para*-position on the *K*-bands of the halogenobenzenes (cf. Table 3). The red-shifts are considerably greater than those to be expected for these substituents on the "receiving" end of the effective electron migration. As will be more fully discussed in a subsequent publication, the corresponding displacements are, *e.g.*, for the methoxyl group in *p*-anisidine

[7] Ungnade, *J. Amer. Chem. Soc.*, 1953, **75**, 432.

10 and 30 Å, for the amino-group in *p*-phenylenediamine 96 and 119 Å, for the iodine atom in *p*-iodoaniline 158 and 123 Å, and for the negatively charged oxygen atom in the dibasic salt of quinol, 65 Å (in water) (cf. Table 3). (They should be even smaller, if the change of polarity due to the electron-attracting halogen atoms is taken into account.)

TABLE 3. *Displacements* (Å) *of the maxima of* K-*bands of* p-R·C_6H_4·X *by* R.

R =	OMe		NH_2		O^-	I	
X	EtOH	C_6H_{14}	EtOH	C_6H_{14}	EtOH	EtOH	C_6H_{14}
F	102	95	266	237	282	190	194
Cl	152	128	315	262	335	229	211
Br	139	110	317	258	319	239	230
I	60	39	227	163	225	141	125
NH_2	10	30	96	119	65 *	158	123

* O^-·C_6H_4·O^- in 1N-sodium hydroxide (and sodium hydrogen sulphite).

The *K*-bands of these halogeno-derivatives are displaced in all series to longer wavelengths in the order F < Cl ≤ Br < I showing that the contribution of the increasing polarisability of the C–Hal electrons is more important than that of the change in the polarity of the substituted system which would require increasing displacements in the reverse order. However, in these series the red-shifts due to the chloro-, bromo-, and iodo-substituents (60—101, 72—108, and 106—158 Å, respectively) are smaller than those observed in the halogenobenzenes, even although the effect due to the C–Hal polarisability is now reinforced by that due to the increased polarity of the substituted system. This confirms that the polarisability of the aromatic C–Hal electrons is appreciably greater in direction towards the carbon atom.

The contribution of the polarity factor is indicated by the slightly greater red-shift of the *K*-band of anisole and the phenoxide ion on introduction of the more strongly electron-attracting chlorine than of bromine, which order has not been observed previously. It should also be responsible for the remarkable observation that the effective electron migration in the halogenodiphenyls is in the opposite direction to that in the halogenobenzenes. This is established not only by the much smaller bathochromic displacements of the *K*-bands on introduction of the chlorine, bromine, and iodine atoms and the blue-shift on introduction of the fluorine atom (cf. below) into diphenyl, but also by the opposing effect of solvents in these two series. The electron-shift in the ground state in the C_6H_5·C group on introduction of the electron-attracting halogen atoms increases its polarisability towards the halogen atom and reduces it in the opposite direction, this contribution resulting in a reversal of the relative polarisabilities of the whole absorbing system. This matter is being further investigated.

As will be shown elsewhere, the only small difference in the position of the *K*-bands of chlorobenzene and bromobenzene (5—8 Å) and the fact that the *p*-bromo-derivatives of aniline, diphenyl, and iodobenzene absorb at slightly longer wavelengths than the corresponding chloro-derivatives (5—15 Å) can be attributed to a small contribution of the complementary electron migration of the transition which in the comparison of very small differences cannot be completely neglected.

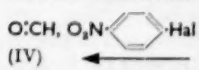
Effect of the Fluorine Atom.—The *K*-band of fluorobenzene in ethanol and hexane appears at 2068 Å, *i.e.*, at longer wavelengths than that of benzene. This is in agreement with observations by Hammond, Price, Teegan, and Walsh,[8] and by Klevens and Zimring [9] for the gaseous state and the heptane solution, respectively, of this compound.

In contrast, the *p*-fluoro-derivatives of diphenyl, anisole, aniline, and iodobenzene in both hexane and ethanol and those of the phenoxide ion in ethanol and water definitely absorb at shorter wavelengths (by 10—38 Å) than the corresponding parent substances. The increase of polarity of the absorbing systems of these compounds in the direction of the effective electron migration of the *K*-band transition should in itself be responsible for a moderate red-shift of the *K*-band. Thus, the blue shifts observed show that the

[8] Hammond, Price, Teegan, and Walsh, *Discuss. Faraday Soc.*, 1950, **9**, 53.
[9] Klevens and Zimring, *J. Chim. physique*, 1952, **49**, 377.

polarisability of the C–F electrons in this direction must be appreciably smaller than that of the C–H electrons, the latter group being only arbitrarily chosen as standard owing to its small polarisability and common occurrence in organic compounds.

p-Halogeno-nitrobenzenes and -benzaldehydes.—The effective electron migration of the *K*-band transition in nitrobenzene, benzaldehyde, and their *p*-halogen derivatives is towards the nitro or carbonyl group, respectively (as in IV). Thus, the *K*-bands appear at appreciably longer wavelengths in ethanol than in hexane, the displacements being smaller in the less polar halogeno-derivatives [for data of the observed displacements (*D*) and those attributable to the C–Hal bonds (*D'*), see Table 2, (vi) and (vii)].



(IV)

Introduction of the halogen atoms into the *p*-position of nitrobenzene and benzaldehyde is responsible for red-shifts increasing in the order F < Cl < Br < I (*D* in ethanol, **27**, **104**, **160**, **345** Å, and **16**, **99**, **146**, **263** Å, respectively). As in the halogenobenzenes, the small blue-shift to be expected from the reduction of the polarity of the substituted system in the ground state is completely masked by the much more important contribution of the polarisability of the C–Hal electrons. In the nitrobenzene derivatives, the displacements to longer wavelengths are greater than in the benzaldehydes, since in the ground state the more strongly electron-attracting nitro-group is responsible for a greater shift of the C–Hal electrons towards the phenyl group, resulting in their enhanced polarisability in this direction.

A comparison of the red-shifts of the *K*-bands in the spectra of the *p*-halogenobenzaldehydes in ethanol (F, **16**; Cl, **99**; Br, **146**; I, **263** Å) with those observed in the spectra of their conjugate acids in concentrated sulphuric acid (F, **40**; Cl, **245**; Br, **377**; I, **768** Å) is significant. The displacements are not only much greater in the latter, but the increases are appreciably enhanced in this order. The magnitude of this effect allows no doubt that the greater electron demand in the conjugate acids is responsible for an electron shift (in the ground state) increasing in the same order C–F < C–Cl < C–Br < C–I, in which the stabilisation energies (" resonance energies ") are known to decrease. This is similar to the observation [10] that on electron demand the stabilisation energies (which are responsible for the Baker–Nathan effect) decrease, but the polarity changes normally increase in the order C–Me < C–Et < C–Pr^{i} < C–Bu^{t}. Our observations show, again, that the relation between bond-energy increases and polarity changes, which is inherent in the interpretation of these effects by the conceptions of mesomerism, hyperconjugation, and other views based on structures involving non-localised bonds, is not even qualitatively valid.

The difficulty, if not impossibility, of explaining electronic spectra with the help of these conceptions is illustrated by the fact that the terminal halogen atoms displace the *K*-bands to longer wavelengths in the order F < Cl $\lesssim$ Br < I, both on the donating and the receiving end of the effective electron migration. In the former case, *i.e.*, in the *p*-halogeno-derivatives of benzene, nitrobenzene, and benzaldehyde, the interpretation of these red-shifts by means of mesomeric or electromeric electron displacements would require and has led to the conclusion that delocalisation increases both in the ground state and the excited state in the order C–F ⟶ C–I.[11] However, the stabilisation energies (" resonance energies ") derived from chemical reactions and equilibria show unambiguously (at least in the ground state) that the mesomeric and electromeric effects, if real, increase in the opposite order. These observations illustrate also the general experience that there is no simple relation between the effect of substituents on the stability of the ground state and the excited states of a molecule respectively.

What is even more important, the participation of the terminal halogen atoms at the receiving end of the effective electron migration of the transition as in the *p*-halogen derivatives of anisole, aniline, diphenyl, iodobenzene, and the phenoxide ion cannot be accounted for, since in these excited states (" resonance " structures indicating) delocalisation cannot even be postulated. This is also true for the blue-shifts on introduction of a fluorine atom. The latter cannot be explained by any polar effects, and

[10] Burawoy and Spinner, *J.*, 1955, 2085.
[11] Murrell and Longuet-Higgins, *Proc. Phys. Soc.*, 1955, *A*, **68**, 329; in this connection see also Price and Walsh, *Proc. Roy. Soc.*, 1947, *A*, **191**, 30, and ref 8, p. 57.

represent conclusive evidence that even the C–H electrons participate in the electron migration of a transition, their polarisability being greater than that of the C–F electrons in this direction.

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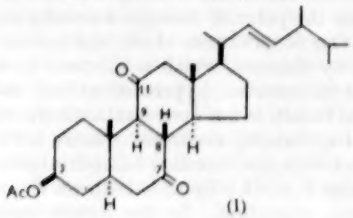
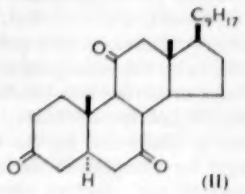
833. *Studies in the Synthesis of Cortisone. Part XIII. The Epimeric 3β : 7-Dihydroxyergost-22-en-11-ones.**

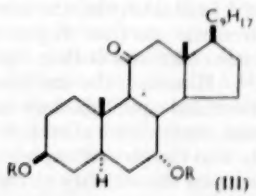
By J. Elks and G. H. Phillipps.

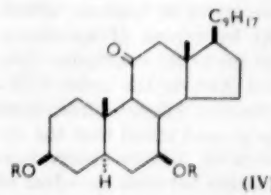
3β-Acetoxyergost-22-ene-7 : 11-dione is reduced by vigorous treatment with alcoholic alkali to 3β : 7α-dihydroxyergost-22-en-11-one and, in much smaller amounts, the 7β-epimer. The same compounds have been prepared by Meerwein–Ponndorf reduction of the 7 : 11-diketone, and their structures have been proved by studies of their optical rotations and of their behaviours under ionic-elimination conditions.

The first methods described for the preparation of 3β-acetoxyergost-22-ene-7 : 11-dione (I) and related 7 : 11-diketones [1] left some doubt as to the configurations of the products at $C_{(8)}$ and $C_{(9)}$: compound (I) was, therefore, submitted to the vigorous treatment with alcoholic potassium hydroxide that is known to epimerise an 8β : 9β-oriented 11-ketone to the more stable 8β : 9α-compound.[2,3] After reacetylation of the crude product a 46% yield was obtained of a pure compound that was not identical with the starting material. Its formulation as a diacetoxyergostenone followed from elementary analysis, from the infrared spectrum, and from its conversion into ergost-22-ene-3 : 7 : 11-trione (II), by alkaline hydrolysis and subsequent chromic oxidation. The 7-oxo-group, rather than the 11-oxo-group, of the diketone (I) had been reduced since (*a*) the product did not yield a 2 : 4-









dinitrophenylhydrazone, (*b*) the diacetate differed from 3β : 11α-diacetoxyergost-22-en-7-one [4] and (*c*) the formation of a diacetate under mild conditions excluded the 3β : 11β-dihydroxy-7-oxo-structure. The dihydroxy-ketone was, therefore, a 3β : 7-dihydroxyergost-22-en-11-one, and we show below that it was the 7α-hydroxy-isomer (III; R = H).

* Part XII, *J.*, 1955, 2807.

[1] Rosenkranz and Sondheimer, *Fortschr. Chem. org. Naturstoffe*, 1953, **10**, 274.

[2] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.

[3] Elks, Evans, Robinson, Thomas, and Wyman, *J.*, 1953, 2933.

The treatment of the diketone (I) with alcoholic alkali gave, in addition to the diol (III; R = H), a very small yield of a compound that we show below to be the epimeric 3β : 7β-dihydroxyergost-22-en-11-one (IV; R = H).

Reduction of 3β-acetoxyergost-22-ene-7 : 11-dione (I) by the Meerwein–Ponndorf procedure gave 3β : 7α-dihydroxyergost-22-en-11-one (III; R = H) as a minor product (16% yield). The major product (60% yield) was an isomer, identical with the minor product of the reduction with alcoholic potassium hydroxide; it was oxidised to ergost-22-ene-3 : 7 : 11-trione (II) and was formulated as the epimeric 7β-hydroxy-compound, *i.e.*, (IV; R = H).

The same two compounds were obtained as their acetates, both in very poor yield, by reduction of 3β-hydroxyergost-22-ene-7 : 11-dione with sodium in propan-2-ol and subsequent acetylation. Barnes and Barton [5] have since described the reduction of the diketone (I) with sodium and propanol to a mixture of ergost-22-ene-3β : 7 : 11α-triols; they attributed the 7β-structure to their major product on the basis of its rotation, but this requires correction. Professor Barton writes, "The calculated [*M*] values recorded by Barnes and Barton are in error; the correct values are −396° and −45° for the 3β : 7α : 11α-triacetoxyergost-22-ene and for the 7β-epimer respectively. The configuration at $C_{(7)}$ of the main sodium–propanol reduction product is therefore 7α, and not 7β as inferred previously."

In the first instance, configurations were assigned to the 7-hydroxy-groups in compounds (III) and (IV) on the basis of their optical rotations (see Table). Of the Δ*M* values found for our four compounds, three are in good agreement with recorded values; the fourth, that for the 7β-acetoxy-compound, has the right sign but is rather low.

It is now well established [6] that treatment of a 7α-hydroxy-steroid with phosphorus oxychloride and pyridine gives the Δ^7-olefin, whereas a 7β-hydroxy-steroid is converted into the 7α-chloro-compound under similar conditions. Both of our compounds (III and IV; R = H) were treated in this way; since the free 3-hydroxy-group was expected to interfere, no attempt was made to isolate pure compounds, but the crude products were

Molecular rotations of the 3β : 7-*dihydroxyergost-22-en*-11-*ones and their diacetates.*

Compound	[*M*]	Δ*M* (7-OH)	Standard values [a]
3β-Hydroxyergost-22-en-11-one	+109° †	—	—
3β : 7α-Dihydroxyergost-22-en-11-one (III; R = H)	+52	−57°	Δ*M* (7α-OH) −59°
3β : 7β-Dihydroxyergost-22-en-11-one (IV; R = H)	+191	+82	Δ*M* (7β-OH) +110
		Δ*M* (7-OAc)	
3β-Acetoxyergost-22-en-11-one	+52 †	—	—
3β : 7α-Diacetoxyergost-22-en-11-one (III; R = Ac)	−95	−147	Δ*M* (7α-OAc) −143
3β : 7β-Diacetoxyergost-22-en-11-one (IV; R = Ac)	+141	+89	Δ*M* (7β-OAc) +208

[a] Barton and Klyne (*Chem. and Ind.*, 1948, 755). Note that the trivial indices used by these authors for the 7-hydroxy-epimers in the *allo*-series must be interchanged (see, *inter al.*, Heymann and Fieser, *Helv. Chim. Acta*, 1952, **35**, 631; Barton, *J.*, 1949, 2174; Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226). More recent examples of 7-hydroxy-compounds give figures that agree well with those of Barton and Klyne, with the exception that in the 3β : 17β-diacetoxy-androstane series, the Δ*M* figures for 7β-hydroxy (+176°) and for 7α-acetoxy (−78°) are anomalous in magnitude, though correct in sign (Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284).

† Determined by us.

treated with alumina and their ultraviolet absorptions were then examined. The product from the alcohol (III; R = H) showed a strong peak at 247 mμ ($E^{1\%}_{1\,cm.}$ 202; cf. ref. 7), whereas that from the epimer (IV; R = H) showed general absorption only. This confirms the assignments of structure made on the basis of rotation evidence, the absorption

[4] Budziarek, Stevenson, and Spring, *J.*, 1952, 4874; Heusser, Anliker, Eichenberger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 936.

[5] Barton and Thomas (with, in part, Thomas), *J.*, 1953, 1842; Barton and Klyne, *Chem. and Ind.*, 1948, 755; Heymann and Fieser, *Helv. Chim. Acta*, 1952, **35**, 631; Barton, *J.*, 1949, 2174.

[6] Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226; Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284; Buser, *ibid.*, 1947, **30**, 1379.

[7] Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 3rd Edn., p. 190.

in the product from the 7α-hydroxy-11-ketone (III) being the result, presumably, of dehydration to the 11-oxo-Δ^7-olefin and migration of the double bond into conjugation.

The reduction of ketones to secondary alcohols by means of alkali alkoxides or alcoholic alkali (which, if the water content is low, exists largely as alkoxide [8]) has been demonstrated in both the steroid [9] and other series [10] (for earlier references see ref. 11); the stereochemistry of the reduction does not, however, appear to have been investigated.

Barton and Rosenfelder [12] have shown that reduction of 3β-acetoxycholestan-7-one with sodium and propan-1-ol gives the 7β(equatorial)- and 7α(axial)-alcohols in the ratio 78 : 22, and this may be taken as an indication of the relative thermodynamic stabilities of the epimeric groups.[13] If the conditions of the reduction of the diketone (I) with alcoholic alkali were sufficiently vigorous to establish a thermodynamic equilibrium at $C_{(7)}$, then the 7β-hydroxy-compound (IV) should predominate in the product. In fact, only 4% of this compound was isolated, whereas the 7α-hydroxy-epimer (III) was obtained in 46% yield. That this was not the result of an equilibration was confirmed when both epimers (III and IV; R = H) were recovered in high yield after being submitted to the conditions used to reduce the diketone (I).

The result, just mentioned, of the reduction of the diketone (I) with alcoholic potassium hydroxide is in striking contrast to the formation of the 7β-hydroxy-epimer (IV) in greatly preponderating amount by the Meerwein–Ponndorf reduction. Although difficult to explain on the earlier view that such hydrogen-transfer processes proceed by a similar mechanism, the difference is explicable on the view [14,15] that the aluminium alkoxides react with carbonyl compounds *via* a cyclic transition state (V), the geometry of which dictates the steric course of the reaction. If reduction by sodium ethoxide occurs as shown in (VI),[15] then, as long as equilibration does not intervene, formation of the axial hydroxy-compound should be favoured, the ethoxide ion having approached from the opposite, less hindered side. This would explain our results and also the formation of 11β-hydroxy-steroids among the products of Wolff–Kishner reduction of 11 : 12-diketones.[16] A further test was made by treating hecogenin acetate (VII; R = Ac, R′ = O) with ethanolic potassium hydroxide under the conditions used in the reduction of the diketone (I). The hindrance at $C_{(11)}$ prevented side-reactions, and the product, after removal of a little unchanged ketone, was 60% of *epi*rockogenin (VII; R = H, R′ = α-OH) and 40% of rockogenin (VII; R = H, R′ = β-OH). This preponderance of the axial 12α-isomer is to be compared with the formation of the 12β-hydroxy-compound as the sole or major product of reduction of hecogenin by hydrogen and a platinum catalyst,[17,18] by sodium and ethanol,[17] or by lithium aluminium hydride.[19]

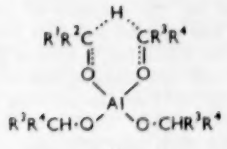
Dutcher and Wintersteiner [9] have shown that 3-oxo-steroids are reduced by alcoholic sodium ethoxide at 180° to mixtures of the 3α- and 3β-hydroxy-compounds in which the equatorial epimers predominate; this, however, is clearly due to establishment of thermodynamic equilibrium under these conditions.[20]

Perhaps related to these reductions by alcoholic alkali is the recent observation by Djerassi *et al.*[21] that 3-oxo-5α-steroids are reduced by ethanol in presence of aged Raney nickel to mixtures of the 3α- and 3β-hydroxy-compounds in which the former (axial)

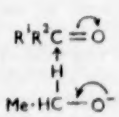
[8] Caldin and Long, *J.*, 1954, 3737.
[9] Dutcher and Wintersteiner, *J. Amer. Chem. Soc.*, 1939, **61**, 1992.
[10] Rubin, *ibid.*, 1944, **66**, 2075; Allen, Jones, and van Allen, *J. Org. Chem.*, 1946, **11**, 268.
[11] Hargreaves and Owen, *J.*, 1947, 750.
[12] Barton and Rosenfelder, *J.*, 1951, 1048.
[13] Barton and Robinson, *J.*, 1954, 3045.
[14] Jackman and Macbeth, *J.*, 1952, 3252; Jackman, Macbeth, and Mills, *J.*, 1949, 2641.
[15] Woodward, Wendler, and Brutschy, *J. Amer. Chem. Soc.*, 1945, **67**, 1425; Doering and Aschner, *ibid.*, 1953, **75**, 393.
[16] Wintersteiner and Moore, *J. Biol. Chem.*, 1946, **162**, 725; Djerassi, Ringold, and Rosenkranz, *J. Amer. Chem. Soc.*, 1954, **76**, 5533.
[17] Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof, *ibid.*, 1947, **69**, 2167.
[18] Mueller, Norton, Stobaugh, Lin Tsai, and Winniford, *ibid.*, 1953, **75**, 4892.
[19] Hirschmann, Snoddy, Hiskey, and Wendler, *ibid.*, 1954, **76**, 4013; Elks, Phillipps, Taylor, and Wyman, *J.*, 1954, 1739.
[20] Windaus, *Ber.*, 1916, **49**, 1724.
[21] Djerassi, Manson, and Gorman, *J. Amer. Chem. Soc.*, 1955, **77**, 4925.

epimers predominate. A hydrogen-transfer mechanism appeared to be operative in this reaction.

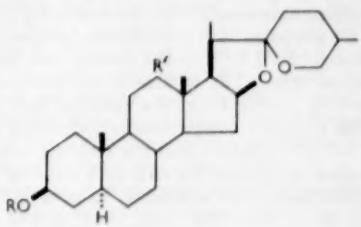
Budziarek, Newbold, Stevenson, and Spring,[22] in preparing the diketone (I) by treatment of 3β-acetoxy-9α : 11α-epoxyergost-22-en-7-one or of 3β : 11α-diacetoxyergosta-8(9) : 22-dien-7-one with strong aqueous-alcoholic potassium hydroxide and subsequent



(V)



(VI)



(VII)

reacetylation, obtained a by-product to which they assigned the empirical formula $C_{32}H_{52}O_5$. The physical constants were similar to those of our 3β : 7α-diacetoxyergost-22-en-11-one (III; R = Ac) and comparison of the melting point and infrared spectrum of our product with those of a sample kindly provided by Prof. F. S. Spring showed them to be identical. The ethoxyl content found by Budziarek *et al.* was presumably due to solvation : the infrared spectrum showed no bands attributable to an ether link.

Experimental

Rotations were determined on *ca.* 1% solutions in $CHCl_3$, unless otherwise stated. M. p.s were taken on a Kofler block. A Perkin-Elmer model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infrared spectra.

Treatment of 3β-Acetoxyergost-22-ene-7 : 11-dione with Alcoholic Potassium Hydroxide.—A solution of 3β-acetoxyergost-22-ene-7 : 11-dione (10 g.) in absolute alcohol (300 ml.) containing potassium hydroxide (60 g.) was refluxed under nitrogen for 18 hr. Most of the alcohol was removed under reduced pressure, the residue was diluted with water to 1 l., and the flocculent precipitate was collected, dried, and heated with acetic anhydride (100 ml.) and pyridine (100 ml.) on the steam-bath for 40 min. After removal of reagents under reduced pressure, the gum crystallised from methanol as yellowish needles (4·8 g., 44%), m. p. 173—177°. Further crystallisation from aqueous ethanol or methanol gave 3β : 7α-*diacetoxyergost-22-en-11-one* as colourless needles, m. p. 175—177°, $[\alpha]_D^{20}$ −18·5° (*c* 1·0) (Found : C, 75·1; H, 9·4; Ac, 15·4; EtO, 0·88. $C_{32}H_{50}O_5$ requires C, 74·7; H, 9·8; 2Ac, 16·7; EtO, 0%). The compound showed only general ultraviolet absorption above 220 mμ, and infrared max. (in CS_2) at 1740 and 1245 (OAc), 1712 (CO),* and 976 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

The methanol mother-liquors from the first crystallisation of the above compound were evaporated to dryness and the residue was chromatographed on alumina (Peter Spence Grade H; 180 g.). The first benzene eluates yielded an oil which, on crystallisation from methanol, gave a further 240 mg. (2%) of 3β : 7α-diacetoxyergost-22-en-11-one, m. p. 174—177°, $[\alpha]_D$ −18° (*c* 0·5). Subsequent benzene eluates, on crystallisation from methanol, gave 3β : 7β-diacetoxyergost-22-en-11-one (145 mg., 1·3%), m. p. 171—173°, $[\alpha]_D$ +26° (*c* 0·4), identical (mixed m. p. and infrared spectrum) with material prepared as described below.

The mother-liquors from these crystallisations were evaporated to dryness, and the residue was hydrolysed with boiling alcoholic potassium hydroxide. Crystallisation of the product from methanol gave 260 mg. (2·8%) of 3β : 7β-dihydroxyergost-22-en-11-one, m. p. 224—226°, $[\alpha]_D$ +44° (*c* 0·4), identified by comparison with a sample prepared as described below.

3β : 7α-*Dihydroxyergost-22-en-11-one.*—3β : 7α-Diacetoxyergost-22-en-11-one (1·5 g.) was boiled with a 4% solution of potassium hydroxide in 80% ethanol for 2 hr. Precipitation with water and crystallisation from aqueous methanol gave 3β : 7α-*dihydroxyergost-22-en-11-one* as

* In Parts XIII—XVIII of this series (this and the following five papers), the infrared structural assignment CO indicates ketone.

[22] Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892.

lustrous plates (1·2 g.), m. p. 197—198°, $[\alpha]_D$ +12·6° (*c* 0·5) (Found : C, 77·7; H, 10·4. $C_{28}H_{44}O_3$ requires C, 78·1; H, 10·8%), infrared max. (in Nujol) at 3350 (OH), 1690 (CO), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

The dihydroxy-compound, on treatment with acetic anhydride and pyridine, gave the original diacetate.

Meerwein–Ponndorf Reduction of 3β-*Acetoxyergost*-22-*ene*-7 : 11-*dione*.—The diketone (10 g.) and crushed aluminium *iso*propoxide (10 g.) were heated together in dry propan-2-ol (100 ml.) under an uncooled reflux condenser leading to a cooled distillation condenser. The mixture was refluxed for 1 hr. and the heating was then increased so that propan-2-ol distilled at about 4 drops per min. The volume of the mixture was kept constant by dropwise addition of fresh propan-2-ol. After 6 hr. the reaction was complete, as shown by the absence of acetone from the distillate (dinitrophenylhydrazone test). One-half of the propan-2-ol was removed under reduced pressure and the residual mixture was diluted with ether (*ca.* 1 l.) and shaken with excess of aqueous tartaric acid solution. Some solid which did not dissolve was collected and crystallised from methanol, to give 3β : 7β-*dihydroxyergost*-22-*en*-11-*one* as lustrous plates (1·5 g.), m. p. 225—228°, $[\alpha]_D$ +44° (*c* 0·5) (Found : C, 78·25; H, 10·6. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·8%), infrared max. (in Nujol) at 3400 (OH), 1688 (CO), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

Removal of solvent from the washed and dried ether solution gave a solid residue which was crystallised from methanol (250 ml.). The first crop (2·8 g.) had m. p. 224—228° and $[\alpha]_D$ +45°, and was identical with the 7β-hydroxy-compound described above. After concentration of the mother-liquors to 100 ml., a second crop (1·8 g., m. p. 210—225°) was obtained which, on recrystallisation, gave a further 1·3 g. of the pure 3β : 7β-dihydroxy-compound (total yield 61%).

The filtrate from the second crop of crystals was diluted with water, and the resulting solid was recrystallised from aqueous methanol, giving fibrous needles (2·3 g.), m. p. *ca.* 180°, which, crystallised from aqueous acetone, gave 3β : 7α-dihydroxyergost-22-en-11-one (1·5 g., 16%), m. p. 198—201°, $[\alpha]_D$ +12·6° (*c* 0·5), identical with the material obtained as described above.

3β : 7β-*Diacetoxyergost*-22-*en*-11-*one*.—3β : 7β-Dihydroxyergost-22-en-11-one (1·0 g.) was warmed on the steam-bath for 1 hr. with acetic anhydride (10 ml.) and pyridine (10 ml.). The solution was poured on ice, and the solid was filtered off, washed with water, and dried. Crystallisation from aqueous methanol gave 3β : 7β-*diacetoxyergost*-22-*en*-11-*one* as colourless needles (1·0 g.), m. p. 172—174°, $[\alpha]_D$ +27·5° (*c* 1·0) (Found : C, 74·6; H, 9·6; Ac, 15·6. $C_{32}H_{50}O_5$ requires C, 74·7; H, 9·8; 2Ac, 16·7%); infrared max. (in CS_2) at 1736 and 1240 (OAc), 1710 (CO), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

Hydrolysis of the diacetate with 4% alcoholic potassium hydroxide gave the 3β : 7β-diol in theoretical yield.

3β-*Hydroxyergost*-22-*ene*-7 : 11-*dione*.—3β-Acetoxyergost-22-ene-7 : 11-dione (10 g.) was boiled under reflux for 2 hr. in ethanol (300 ml.) containing potassium hydroxide (3·0 g.). Dilution with water gave a flocculent precipitate which crystallised from aqueous alcohol. 3β-*Hydroxyergost*-22-*ene*-7 : 11-*dione* separated as needles (7·5 g.), m. p. 194—196°, $[\alpha]_D$ −23° (*c* 1·0) (Found : C, 78·85; H, 10·7. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·35%), infrared max. (in Nujol) at 3600 (OH), 1700 (CO), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

Reacetylation with acetic anhydride and pyridine gave material identical with the original acetoxy-compound.

Ergost-22-*ene*-3 : 11 : 20-*trione*.—(a) *From* 3β-*hydroxyergost*-22-*ene*-7 : 11-*dione*. The diketone (1·0 g.) in acetic acid (75 ml.) was treated with a 2% solution of chromic anhydride in glacial acetic acid (12·0 ml.) and left at room temperature for 18 hr. After addition of a few drops of methanol to destroy excess of chromic acid, the solvent was removed under reduced pressure and the residue was evaporated twice with benzene to remove traces of acetic acid. The residue was then extracted with benzene (3 × 50 ml.), and the benzene solution filtered. The filtrate was reduced to 50 ml. and run on to alumina (acid-washed; 30 g.). Elution with benzene and crystallisation from aqueous methanol gave the 3 : 7 : 11-*trione* as plates, m. p. 187—189°, $[\alpha]_D$ −8° (*c* 1) (Found : C, 78·8; H, 9·7. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%), infrared max. (in CS_2) at 1720—1710 (CO) and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

(b) *From* 3β : 7β-*dihydroxyergost*-22-*en*-11-*one*. The dihydroxy-ketone (0·5 g.) in glacial acetic acid (50 ml.) was oxidised by addition of a 2% solution of chromic anhydride in glacial acetic acid (12·0 ml.). Isolated as in (a), ergost-22-ene-3 : 7 : 11-trione (0·3 g.) had m. p. 187—189° and $[\alpha]_D$ −8°; its identity with material prepared as in (a) was established by mixed m. p. and by comparison of infrared spectra.

(c) *From* 3β : 7α-*dihydroxyergost-22-en*-11-*one*. The dihydroxy-ketone (0·25 g.) in glacial acetic acid (50 ml.) was oxidised by addition of a 2% solution of chromic anhydride in glacial acetic acid (6·0 ml.). Isolated as in (a), ergost-22-ene-3 : 7 : 11-trione had m. p. 187—189° and $[\alpha]_D$ −8°, and was shown to be identical with material prepared as in (a).

Reduction of 3β-*Hydroxyergost-22-ene-7* : 11-*dione with Sodium in Propan-2-ol*.—To a solution of 3β-hydroxyergost-22-ene-7 : 11-dione (3·0 g.) in warm propan-2-ol (30 ml.) pieces of sodium (6·0 g.) were gradually added. The mixture was then refluxed for 2 hr., by which time all the sodium had dissolved. After removal of most of the solvent under reduced pressure, water (*ca.* 100 ml.) was added to the residue. The precipitate was dried and heated on the steam-bath for 20 min. with acetic anhydride (25 ml.) and pyridine (25 ml.). After removal of the acetylating mixture under reduced pressure the residue was evaporated twice with methanol and twice with benzene. The gummy residue was chromatographed in benzene on alumina (90 g.; acid-washed; Peter Spence grade "H"). Evaporation of the benzene eluate (200 ml.) left a gum (0·5 g.), which crystallised from aqueous methanol in needles (0·3 g.), m. p. 173—177°, $[\alpha]_D$ −17°. The infrared spectrum and a mixed m. p. determination showed the compound to be 3β : 7α-diacetoxyergost-22-ene-7 : 11-dione. The following 3 : 1-benzene–ether eluate (200 ml.) gave a gum (1·0 g.) which, after three crystallisations from aqueous methanol, yielded needles (0·25 g.), m. p. 173—177° and $[\alpha]_D$ +25°, whose infrared spectrum and mixed m. p. showed the substance to be 3β : 7β-diacetoxyergost-22-ene-7 : 11-dione.

Treatment of the 7-*Hydroxy-compounds with Phosphorus Oxychloride*.—(*a*) 3β : 7α-Dihydroxyergost-22-en-11-one (0·5 g.) in dry pyridine (4 ml.) was heated with phosphorus oxychloride (2 ml.) in pyridine (3·5 ml.) for 2 hr. at *ca.* 100°. After being cooled the mixture was diluted to *ca.* 80 ml. with ether and treated with ice (*ca.* 10 g.). The ether solution was washed with sodium hydrogen carbonate solution, water, N-hydrochloric acid, and water, and evaporated. The gummy residue was shaken in light petroleum (50 ml.) with alumina (15 g.; Peter Spence Grade O). After 2 hr., the alumina was filtered off and washed with methanol (3 × 50 ml.). The solvents were removed from the combined petroleum and methanol filtrates under reduced pressure, to leave a gum (0·34 g.), whose ultraviolet spectrum (in EtOH) showed a maximum at 247 mμ ($E^{1\%}_{1cm.}$ 202).

(*b*) 3β : 7β-Dihydroxyergost-22-en-11-one (0·5 g.), treated as in (*a*), finally gave a yellow gum (0·39 g.), the ultraviolet spectrum of which showed general absorption only.

Reduction of Hecogenin Acetate with Alcoholic Potassium Hydroxide.—Hecogenin acetate (2·0 g.) was boiled under reflux for 18 hr. with potassium hydroxide (12·0 g.) in dry ethanol (60 ml.). The brown solution was poured into water, and the precipitated solid (1·85 g.) was filtered off and boiled under reflux for 1 hr. with Girard reagent P (1·0 g.) in ethanol (40 ml.) containing acetic acid (4·5 ml.); the solution was poured into a solution of sodium hydrogen carbonate (7 g.) in water (*ca.* 300 ml.), and the precipitate was extracted into ether. The extract was washed with water, dried ($MgSO_4$), and evaporated, to leave a solid residue (1·45 g.), m. p. 204—210°. The infrared spectrum and the rotation (−40° in acetone) of this material were consistent with its being a mixture of rockogenin (33%) and *epi*rockogenin (67%).

With acetic anhydride and pyridine at 100° it gave a mixture of rockogenin diacetate and *epi*rockogenin diacetate, $[\alpha]_D$ −33° (*c* 1·19 in acetone) (corresponding to 39% and 61% of the respective isomers [19]), after crystallisation from methanol (Found: C, 72·1; H, 9·4. Calc. for $C_{31}H_{48}O_6$: C, 72·05; H, 9·4%). Paper-chromatography of the mixed diols corroborated the above evidence of its constitution (for method, see ref. 23).

The aqueous layer from the Girard separation deposited 0·36 g. of crude hecogenin on acidification.

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[19] Brooks, Hunt, Long, and Mooney, *J.*, in the press.

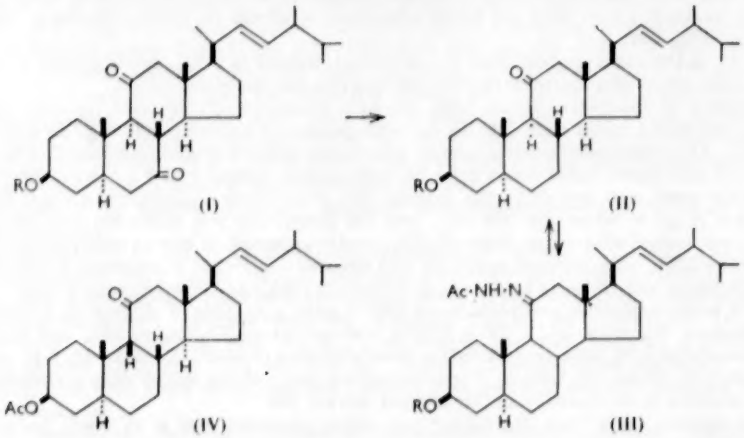
834. *Studies in the Synthesis of Cortisone. Part XIV.* Acetylhydrazones and Azines of Steroidal Ketones.*

By J. Elks and G. H. Phillipps.

In the preparation of 3β-acetoxyergost-22-en-11-one from 3β-acetoxyergost-22-ene-7 : 11-dione by Wolff–Kishner reduction and subsequent acetylation a by-product has been isolated and shown to be 3β-acetoxyergost-22-en-11-one acetylhydrazone. Acetylhydrazones and azines of some other steroidal ketones have been prepared for comparison of their infrared and ultraviolet spectra with those of the by-product.

The preparation of 3β-hydroxyergost-22-en-11-one (II; R = H) from 3β-acetoxyergost-22-ene-7 : 11-dione (I; R = Ac) by Wolff–Kishner reduction has been described [1,2] as part of procedures for the synthesis of cortical steroids from ergosterol. We have found that a method similar to that of Chamberlin *et al.*,[2] but done at 160° rather than 200° and involving chromatography of the acetylated crude product on alumina, gives the 11-ketone (II; R = Ac) in 65—70% yield and also some 7% of a more strongly adsorbed material.

The formulations of the by-product as the acetylhydrazone (III; R = Ac) of 3β-acetoxyergost-22-en-11-one, and of its alkaline hydrolysis product [which can be reacetylated to (III; R = Ac)] as (III; R = H) follow from elementary analysis and from the conversion of the acetylhydrazone acetate (III; R = Ac) into the ketone acetate (II; R = Ac) in low yield by hydrolysis with aqueous-alcoholic sulphuric acid or with pyruvic acid in acetic acid and subsequent acetylation. Further, the ketone (II; R = Ac) gave a low yield of the acetylhydrazone (III; R = Ac), under conditions similar to



those used for the Wolff–Kishner reduction. Attempts to form the acetylhydrazone (III; R = Ac) from the ketone (II; R = Ac) by acethydrazide in refluxing alcohol or in diethylene glycol at 220° gave only unchanged starting material; the ketone was also unaffected by hydrazine hydrate in hot acetic acid.

The lack of reactivity of the 11-keto-group to carbonyl reagents [3] is well established; apart from reduction to 11-hydroxyl the only recorded reactions are Wolff–Kishner

* Part XIII, preceding paper.

[1] Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106.
[2] Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1953, **75**, 3477.
[3] Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Edn., Reinhold Publ. Corp., New York, N.Y., 1949, pp. 409—410.

reduction,[1,4] formation of an ethylene ketal under forcing conditions,[5] and possibly Clemmensen reduction.[6] Although the 11-ketones of the 9β-hydrogen series have been reported as unreactive to carbonyl reagents,[7] a derivative of such a compound (containing also a 7 : 8-double bond, which may be of some significance) has since been prepared.[8]

The possibility was considered that the acetylhydrazone was a derivative of the 9β : 11-ketone (IV), which might exist in equilibrium with its 9α-epimer (II) under the enolising alkaline conditions. However, the ketone group in (IV) also failed to react with acethydrazide in refluxing alcohol. It therefore seemed most probable that the acetylhydrazone had structure (III; R = Ac) and that it arose from the 11-hydrazone, which itself must be an intermediate in the Wolff–Kishner reduction of the 7 : 11-diketone (I; R = Ac) to ergost-22-en-3β-ol.[1] That such a derivative would be expected to have infrared and ultraviolet absorption of the type found has been confirmed by examination of the spectra of other acetylhydrazones.

3β-Acetoxyergost-22-ene-7 : 11-dione (I; R = Ac), with acethydrazide in alcohol, gave a 7-acetylhydrazone, the reaction being slower than the formation of cholestanone acetylhydrazone. With hydrazine hydrate in acetic acid the ketones (I; R = H and Ac) gave the 7-azines, and cholestanone the 3-azine. The second of these azines was unstable in hot acetic acid, the ketone being re-formed. The 3β-hydroxyl group of the azine from the alcohol (I; R = H) could be acetylated, the molecule being otherwise stable to such conditions, unlike the azine from cholestanone, which gave a mixture of cholestanone and its acetylhydrazone.

Spectra of the Acetylhydrazones.—Acetylhydrazones of steroids have been prepared both directly [9] and from semicarbazones,[10] but the only available information about their infrared spectra is that pregnenolone acetylhydrazone and progesterone bisacetylhydrazone show bands at 1675 and 1677 cm.$^{-1}$, respectively. We find that the acetylhydrazones of acetone, cholestan-3-one, 3β-acetoxyergost-22-ene-7 : 11-dione, and the compounds (III; R = H and Ac) all show bands in their infrared spectra (in CS_2 solution or as Nujol mulls) at *ca.* 3150 cm.$^{-1}$ (N–H) and *ca.* 1665 cm.$^{-1}$ (C=O and C=N). The "amide II" band at *ca.* 1540 cm.$^{-1}$, probably best attributed [11] to C–N, was, however, present only in the spectra of Nujol mulls of the derivatives of acetone and cholestanone. Its absence from the spectra of the derivatives of the 7- and 11-ketones may possibly be explained, on steric grounds, as due to prevention of the assumption of partial double-bond character by the amido-carbon–nitrogen bond.[11] Nevertheless, the 7-semicarbazone of 3β-acetoxyergost-22-ene-7 : 11-dione (I) in Nujol does show an amide II band at 1568 cm.$^{-1}$.

The ultraviolet spectra of acetylhydrazones have been described, but for the only one comparable with our own, namely, acetone acetylhydrazone, the range examined just missed the position of maximum absorption.[12] The acetylhydrazone of pregnenolone has been reported to exhibit a maximum at 235 mμ, and that of progesterone at 242 and 275 mμ, but the extinction coefficients were not given.[9] We found, in our steroidal acetylhydrazones, as well as in that of acetone, that maxima appear at two wavelengths, *ca.* 215 and 235 mμ, and that compounds showing a maximum at only one position show an inflexion at the other. Thus the acetone and the cholestanone derivatives show a maximum at *ca.* 235 mμ, and the 11-ketone derivatives at *ca.* 215 mμ, whereas the 7-ketone derivative shows a double maximum. This variation, as with that in the infrared spectra, may be due to steric factors, but the number of examples is too small to give conclusive evidence on the point.

[4] Moffett and Hunter, *J. Amer. Chem. Soc.*, 1951, **73**, 1973; Fieser, Herz, and Wei-Yuan Huang, *ibid.*, p. 2397; Fieser, Wei-Yuan Huang, and Babcock, *ibid.*, 1953, **75**, 116; Fieser and Wei-Yuan Huang, *ibid.*, p. 5356; Barton, Ives, and Thomas, *J.*, 1955, 2056.
[5] Magerlein and Levin, *J. Amer. Chem. Soc.*, 1955, **77**, 1904.
[6] Reichstein, *Helv. Chim. Acta*, 1939, **19**, 979; Steiger and Reichstein, *ibid.*, 1938, **21**, 161.
[7] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.
[8] Inhoffen and Mengel, *Chem. Ber.*, 1954, **87**, 146.
[9] Reich, Sanfilippo, and Crane, *J. Biol. Chem.*, 1952, **198**, 713.
[10] Turner, *J. Amer. Chem. Soc.*, 1947, **69**, 875.
[11] Letaw and Gropp, *J. Chem. Phys.*, 1953, **21**, 1621; Freedman, *J. Amer. Chem. Soc.*, 1955, **77**, 6003; Bellamy, "Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 185.
[12] Grammaticakis, *Bull. Soc. chim. France*, 1948, 973.

Spectra of the Azines.—The ultraviolet absorptions of a few simple azines have been published. The closest analogy with our azines is to be found in those from acetaldehyde [$\lambda_{max.}$ 208 mμ (ε 10,000 in EtOH)] and butyraldehyde [$\lambda_{max.}$ 205 (ε 13,000) and 208 mμ (ε 11,500 in EtOH)].[13] Azines of steroidal ketones have been described,[14] but the absorption in this region was not given. We find that the azines of cholestanone, 3β-hydroxyergost-22-ene-7 : 11-dione, and 3β-acetoxyergost-22-ene-7 : 11-dione show a main maximum at *ca.* 213 mμ (ε *ca.* 20,000).

In their infrared spectra these azines are free from N–H absorption and show a weak band at *ca.* 1635 cm.$^{-1}$, attributed to C=N. The azine from œstrone [14] showed a band at 1653 cm.$^{-1}$, but the different position is readily accounted for since it is a derivative of a 5-membered ring ketone.

Experimental

For general experimental information see Part XIII.

Wolff–Kishner Reduction of 3β-*Acetoxyergost*-22-*ene*-7 : 11-*dione* (I; R = Ac).—The diketone (50 g.), sodium hydroxide (43 g.), diethylene glycol (430 ml.), and 90—95% hydrazine hydrate (15·5 ml.) were heated so that the temperature was raised to 160° during 1 hr., and held at 160° for a further 2 hr. A little water and hydrazine hydrate distilled during the reaction. The product was isolated by gradual addition of water (*ca.* 2 l.) to the stirred mixture at *ca.* 100°, and filtration of the flocculent precipitate after cooling. The crude total product was dried and then acetylated for 15 min. in boiling acetic anhydride (250 ml.). Most of the anhydride was removed by distillation *in vacuo*, and the residue treated twice with methanol to remove the rest and twice with benzene, the solvent being removed each time *in vacuo*.

The crude oily acetate was chromatographed in benzene on alumina (Peter Spence, Type H; 750 g.). Elution with benzene and crystallisation from methanol gave 3β-acetoxyergost-22-en-11-one (II; R = Ac) (31·2 g., 64·3%), m. p. 123—125°, $[\alpha]_D$ +11·5°. Heusser *et al.*[1] give m. p. 125—126°, $[\alpha]_D$ +12·5°, and Chamberlin *et al.*[2] m. p. 129—131°, $[\alpha]_D$ +11·9°. After elution of uncrystallisable oils by ether–benzene, methanol eluted 3β-*acetoxyergost*-22-*en*-11-*one* 11-*acetylhydrazone*, which crystallised from methanol and then acetic acid as needles (4 g., 7·3%), m. p. 202—204°, $[\alpha]_D$ +71° (Found : C, 74·8; H, 10·1; N, 5·5. $C_{33}H_{52}O_3N_2$ requires C, 75·0; H, 10·2; N, 5·5%), $\lambda_{max.}$ (in EtOH) 217·5 mμ (ε 14,000), $\lambda_{infl.}$ 232—236 mμ (ε 10,500), $\nu_{max.}$ (in CS_2) 3200 and 3100 (NH), 1730 and 1242 (OAc), 1666 (CO·NH), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

Hydrolysis of the acetate for 18 hr. with boiling 10% aqueous-alcoholic potassium hydroxide gave the *alcohol* which crystallised from methanol or ethanol as needles, m. p. 216—218°, $[\alpha]_D$ +81° (Found : C, 76·4; H, 10·7; N, 5·7. $C_{30}H_{50}O_2N_2$ requires C, 76·5; H, 10·7; N, 6·0%), $\lambda_{max.}$ (in EtOH) 218 mμ (ε 13,500), $\lambda_{infl.}$ 234—236 mμ (ε 10,080), $\nu_{max.}$ (in CS_2) 3640 (OH), 3200, 1666, and 970 cm.$^{-1}$.

The alcohol was re-acetylated by acetic anhydride in pyridine at 100° to the acetate (III; R = Ac).

Formation of the Acetylhydrazone from 3β-*Acetoxyergost*-22-*en*-11-*one*.—3β-Acetoxyergost-22-en-11-one (4·0 g.), sodium hydroxide (3·5 g.), diethylene glycol (35 ml.), and hydrazine hydrate (4·0 ml.) were heated at 150° for 2 hr. The cooled solution, from which a small amount of white solid had separated, was diluted to *ca.* 400 ml. with water, and the precipitate was collected, washed with water, and dried. The crude product was acetylated at 100° for 20 min. in acetic anhydride (25 ml.) and pyridine (25 ml.), then evaporated *in vacuo*. The residue was chromatographed in benzene on alumina (Peter Spence, Type H; 30 g.). The benzene eluate contained unchanged starting material (3·2 g., 80%). Elution with 1 : 1 ether–methanol and crystallisation from acetic acid (10 ml.) gave the acetylhydrazone (III; R = Ac) as needles (0·34 g., 7·5%), m. p. 202—204°, $[\alpha]_D$ +70° (*c* 0·9), with an infrared spectrum identical with that of the nitrogenous by-product of the Wolff–Kishner reduction. A mixed m. p. was undepressed.

Acid Hydrolysis of 3β-*Acetoxyergost*-22-*en*-11-*one* 11-*Acetylhydrazone*.—(*a*) The acetylhydrazone (2·0 g.) was refluxed for 2 hr. in 80% alcohol (50 ml.) with concentrated sulphuric acid (5 ml.). The gummy product was isolated by precipitation with water and reacetylated with acetic anhydride in pyridine at 100°. The acetylating mixture was removed *in vacuo* and the residue chromatographed in benzene on alumina (Peter Spence, Type O; 30 g.). Elution

[13] Barany, Braude, and Pianco, *J.*, 1949, 1898.
[14] Cohen, Bates, and Liebermann, *J. Amer. Chem. Soc.*, 1952, **74**, 3938.

with benzene and crystallisation from aqueous methanol gave 3β-acetoxyergost-22-en-11-one (II; R = Ac) as needles (50 mg., 2·8%), m. p. and mixed m. p. 118—121°. The infrared spectrum of the product showed that it was slightly impure.

(*b*) A mixture of the acetylhydrazone (2·0 g.), 90% pyruvic acid (6·0 g.), and sodium acetate (6·0 g.) in glacial acetic acid (60 ml.) was refluxed for 18 hr. The dark solution was poured into water (250 ml.), and the tarry product separated by filtration. A chloroform solution of the product was washed with water and dried (Na_2SO_4). The chloroform was removed *in vacuo*, and the residue purified as in (*a*), giving 3β-acetoxyergost-22-en-11-one as needles (100 mg., 5·6%), m. p. and mixed m. p. 117—122°, $[\alpha]_D$ +13°, slightly impure (infrared spectrum).

Cholestan-3-one Azine.—A solution of cholestanone (0·5 g.) in warm acetic acid (15 ml.) was treated with 90—95% hydrazine hydrate (1 ml.). The crystalline precipitate which was formed immediately was collected and washed with a little acetic acid. Crystallisation from 1 : 1 methanol–ethyl acetate (50 ml.) gave the *azine* as prisms, m. p. 222—226° (decomp.), $[\alpha]_D$ +63° (Found: C, 84·3; H, 11·9; N, 3·4. $C_{54}H_{92}N_2$ requires C, 84·4; H, 12·0; N, 3·6%), $\lambda_{max.}$ (in EtOH) 211·5 (ε 21,100) and 234 mμ (ε 5850), $\nu_{max.}$ (in CS_2) 1635 (C=N), and 1375 and 1360 cm.$^{-1}$ (CMe_2).

3β-*Acetoxyergost-22-ene-7* : 11-*dione* 7-*Azine.*—Reaction of 3β-acetoxyergost-22-ene-7 : 11-dione with hydrazine as in the preceding experiment and crystallisation of the crude product from ethyl acetate gave the 7-*azine* as needles, m. p. 300—305° (decomp.), $[\alpha]_D$ −230° (Found: C, 76·5; H, 9·6; N, 3·1. $C_{66}H_{92}O_4N_2$ requires C, 77·0; H, 9·9; N, 3·0%), $\lambda_{max.}$ (in EtOH) 213 mμ (ε 21,500), $\nu_{max.}$ (in CS_2) 1732 and 1240 (OAc), 1708 (CO), 1632 (C=N), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

When a similar mixture was heated at 100° for 2 hr. the azine redissolved and the product was unchanged starting material.

3β-*Hydroxyergost-22-ene-7* : 11-*dione* 7-*Azine.*—Reaction of 3β-hydroxyergost-22-ene-7 : 11-dione with hydrazine as in the preceding experiments and crystallisation of the crude product from methanol gave the 7-*azine* as plates, m. p. 260—270° (decomp.), $[\alpha]_D$ −229° (Found: C, 79·0; H, 10·4; N, 3·7. $C_{54}H_{88}O_4N_2$ requires C, 78·9; H, 10·4; N, 3·3%), $\lambda_{max.}$ (in EtOH) 214·5 mμ (ε 20,000), $\nu_{max.}$ (in CS_2) 3630 and 1024 (OH), 1709 (CO), 1635 (C=N), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

Acetylation of the azine (1·0 g.) with acetic anhydride in pyridine at 100° and crystallisation of the product from ethyl acetate gave the 3β-acetoxy-7-azine as needles (0·9 g.), m. p. 315°, $[\alpha]_D$ −230°, with an infrared spectrum identical with that of the product of the previous experiment.

Acetone Acetylhydrazone.[10]—This had m. p. 138°, and showed $\lambda_{infl.}$ (in EtOH) at 210 mμ (ε 7900) and $\lambda_{max.}$ at 229·5 mμ (ε 10,700), $\nu_{max.}$ (in CS_2) 3200 (NH), 1668 (CO·NH), and 1386 and 1362 cm.$^{-1}$ (CMe_2).

Cholestan-3-one Acetylhydrazone.—(*a*) A solution of cholestanone (0·4 g.) and acethydrazide (0·4 g.) in alcohol (40 ml.) was refluxed for 30 min. The *acetylhydrazone* separated on cooling as needles (0·3 g.), m. p. 223—225°, $[\alpha]_D$ +30° (Found: C, 78·9; H, 11·2; N, 6·6. $C_{29}H_{50}ON_2$ requires C, 78·7; H, 11·4; N, 6·3%), $\lambda_{infl.}$ (in EtOH) 211—218 mμ (ε 9100), $\lambda_{max.}$ 234·5 mμ (ε 10,400), $\nu_{max.}$ (in CS_2) 3200 and 3100 (NH), and 1666 cm.$^{-1}$ (CO·NH).

(*b*) A solution of cholestanone azine (500 mg.) in acetic anhydride (10 ml.) and pyridine (10 ml.) was heated at 100° for 30 min., then evaporated *in vacuo*, and the residue crystallised from methanol to give cholestanone acetylhydrazone as needles (170 mg.), m. p. 219—221°, $[\alpha]_D$ +30°, with an infrared spectrum identical with that of material prepared by method (*a*). The mother-liquors from the crystallisation gave a second crop on dilution with water, which, crystallised from aqueous methanol, gave cholestanone as prisms, m. p. 130—131°, $[\alpha]_D$ +40°, with an infrared spectrum identical with that of authentic material.

3β-*Acetoxyergost-22-ene-7* : 11-*dione* 7-*Acetylhydrazone.*—A solution of 3β-acetoxyergost-22-ene-7 : 11-dione (5·0 g.) and acethydrazide (3·5 g.) in ethanol (150 ml.) was refluxed for 16 hr., and water (5 ml.) was then added. The crystals which separated on cooling were collected, washed, and dried to give the crude product (4·0 g.), m. p. 240—250°. Recrystallisation from methanol gave the 7-*acetylhydrazone* as needles, m. p. 249—250°, $[\alpha]_D$ −180° (Found: C, 73·2; H, 9·2; N, 5·3. $C_{33}H_{50}O_4N_2$ requires C, 73·0; H, 9·6; N, 5·3%), $\lambda_{max.}$ (in EtOH) 217·5 (ε 11,900) and 234 mμ (ε 12,400), $\nu_{max.}$ (in CS_2) 3200 and 3100 (NH), 1732 and 1240 (OAc), 1708 (CO), 1666 (CO·NH), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

3β-*Acetoxyergost-22-ene-7* : 11-*dione* 7-*Semicarbazone.*—A solution of the diketone (2·0 g.), semicarbazide hydrochloride (2·0 g.), and crystalline sodium acetate (2·0 g.) in alcohol (90 ml.) and water (10 ml.) was refluxed for 90 min. The product, which separated during the reaction,

was collected, washed with aqueous alcohol, and recrystallised from aqueous alcohol, to give the 7-*semicarbazone* as needles (1·2 g.), m. p. 259—263° (decomp.), $[\alpha]_D$ −214° (Found : C, 70·8; H, 9·1; N, 7·9. $C_{31}H_{49}O_4N_3$ requires C, 70·6; H, 9·4; N, 8·0%), $\lambda_{max.}$ (in EtOH) 205 (ε 10,000) and 230·5 mμ (ε 13,000), $\nu_{max.}$ (in $CHBr_3$) 3550, 3400, 3200, 1678, and 1578 (NH·CO·NH_2), 1710 and 1250 (OAc), and 1700 $cm.^{-1}$ (CO).

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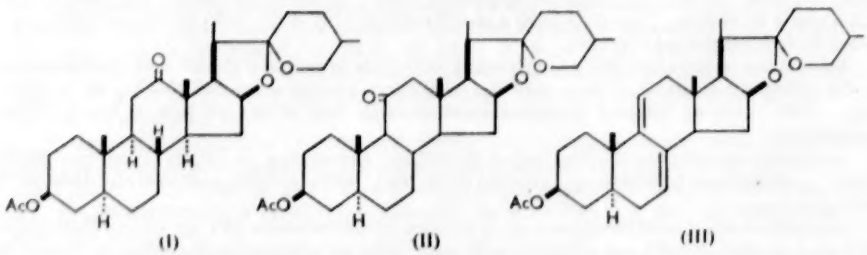
835. *Studies in the Synthesis of Cortisone. Part XV.* Improvements in the Conversion of Hecogenin into 3β : 12β-Diacetoxy-5α : 25D-spirostan-11-one † and a Study of the Isomeric 11 : 12-Ketols.‡*

By J. ELKS, G. H. PHILLIPPS, T. WALKER, and L. J. WYMAN.

Study of the conversion of hecogenin acetate into 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one *via* 11 : 23-dibromohecogenin acetate has made possible an overall yield of 77%.

Some other 11 : 12-ketols of the spirostan series have been prepared and certain of their reactions examined.

THE occurrence of hecogenin in the waste-products from sisal manufacture [1] makes it an attractive starting material for the synthesis of cortisone and related steroid hormones, and methods have been described for converting hecogenin acetate (I) into 11-oxotigogenin acetate (II) [2,3,4] and 3β-acetoxy-5α-25*D*-spirosta-7 : 9(11)-dien † (III),[5] both of which



have in turn been converted into cortisone.[6,7] However, all of these methods leave something to be desired in yield and the number of stages.

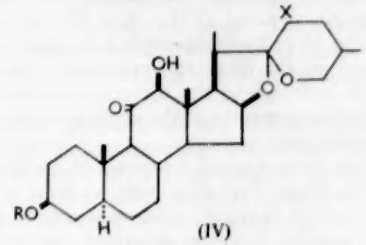
The method used in the bile-acid series by Borgstrom and Gallagher [8,9] for transferring an oxygen atom from $C_{(12)}$ to $C_{(11)}$ involves replacement of the 12β-hydroxy-group in a 12β-hydroxy-11-ketone by bromine, and it cannot be applied to 3-monoesters (IV; X = H) of 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one because the spirostan side-chain is

* Part XIV, preceding paper. † The term "25*D*-spirostan" is used, in this and the following paper, to mean the same configuration at $C_{(20)}$, $C_{(22)}$, and $C_{(25)}$ as that of the naturally occurring "isosapogenins." It is, therefore, synonymous with the older, but now untenable, term "22*a*-spirostan."

‡ Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Callow, Cornforth, and Spensley, *Chem. and Ind.*, 1951, 699; Spensley, *ibid.*, 1952, 426.
[2] Cornforth, Osbond, and Phillipps, *J.*, 1954, 907.
[3] Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241.
[4] Djerassi, Ringold, and Rosenkranz, *J. Amer. Chem. Soc.*, 1954, **76**, 5533.
[5] Hirschmann, Snoddy, and Wendler, *ibid.*, 1953, **75**, 3252.
[6] Rosenkranz and Sondheimer, *Fortschr. Chem. org. Naturstoffe*, 1953, **10**, 274.
[7] (*a*) Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807; (*b*) Barton, Evans, Hamlet, Jones, and Walker, *J.* 1954, 747; (*c*) Chamberlin and Chemerda, *J. Amer. Chem. Soc.*, 1955, **77**, 1221; (*d*) Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[8] Borgstrom and Gallagher, *J. Biol. Chem.*, 1949, **177**, 951.
[9] Hershberg, Herzog, Coan, Weber, and Jevnik, *J. Amer. Chem. Soc.*, 1952, **74**, 2585.

attacked by phosphorus tribromide.[4,10] The corresponding *allo*pregnan-20-ones (V; R = H and Ac) have been prepared from (IV; X = H),[10,11,12] but there is no report of the removal of the 12β-substituents from them.



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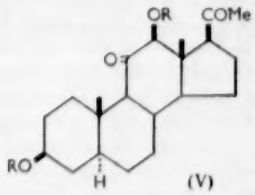

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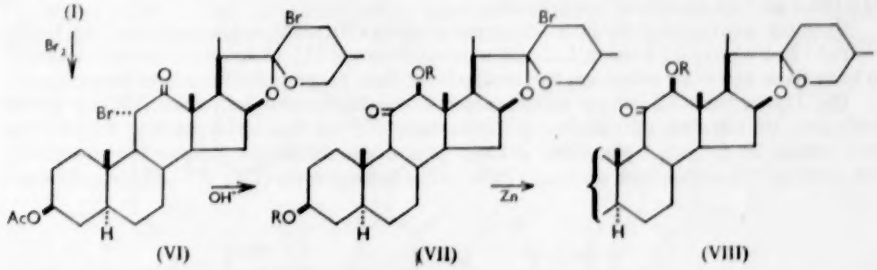
In the search for a more convenient method of passing from hecogenin acetate (I) to the 11-oxo-compound (II), we have re-investigated both the preparation and the reduction of 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (VIII; R = H) and its derivatives. The successful outcome of the second of these studies is described in the next paper; we deal here with improvements in the preparation of the ketone (VIII) and with certain related topics.

Hecogenin acetate (I) has been converted into 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (VIII; R = H) by bromination, treatment of the resulting 11 : 23-dibromo-compound with alkali, and removal of the alkali-stable 23-bromine atom with zinc,[9,10] but the yields were not very high. For our initial experiments we prepared the pure 11α : 23-dibromo-compound (VI). Bromination of hecogenin acetate in chloroform [2,5] led to rather erratic results, and we found dioxan, carbon tetrachloride, or benzene more satisfactory.



From a bromination in carbon tetrachloride a small yield of an isomeric dibromohecogenin acetate was also isolated which, for the following reasons, we believe to be the $C_{(23)}$-isomer of the known compound (VI): (*a*) hecogenin acetate was regenerated by treatment with zinc, (*b*) the carbonyl band in the infrared spectrum suggested the presence of the equatorial 11α-bromine atom,[13,14] and the absorption in the 800—1100 cm.$^{-1}$ region (characteristic of the spiroketal system) differed from that of both compounds (I) and (VI),[13] (*c*) dehydrobromination with collidine gave a bromo-9(11)-dehydrohecogenin acetate ($\lambda_{max.}$ 237·5 mμ), which differed from that obtained in a similar way from the dibromide (VI), but agreed in its properties with the "23*b*-bromo-9(11)-dehydrohecogenin acetate" described by Mueller and Norton.[15] It should be said that there is no evidence positively ruling out the possibility that the bromo-compounds of the new series have the bromine atom at $C_{(20)}$, but we propose nevertheless to adopt Mueller and Norton's convention.

[10] Mueller, Norton, Stobaugh, Lin Tsai, and Winniford, *J. Amer. Chem. Soc.*, 1953, **75**, 4892.
[11] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303.
[12] Martinez, Ringold, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1953, **75**, 239.
[13] Dickson and Page, *J.*, 1955, 447.
[14] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[15] Mueller and Norton, *ibid.*, p. 749.

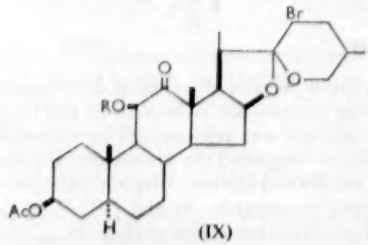
Treatment of 11α : 23*a*-dibromohecogenin acetate (VI) with methanolic potassium hydroxide under the conditions used by Djerassi *et al.*[11] gave a crude 23-bromo-ketol, of which 15% could be extracted by Girard reagent P; this " ketonic fraction " has been identified as 23*a*-bromo-3β : 11β-dihydroxy-5α : 25*D*-spirostan-12-one (see below). The unreactive portion was essentially the required ketol (VII; R = H), for acetylation followed by debromination converted it into 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one (VIII; R = Ac) in some 50% yield (based on the dibromo-compound). An additional complication in the use of this method of hydrolysing the dibromo-compound was the occurrence of dehydrobromination, the ultraviolet spectra of the crude products indicating the presence of up to 10% of 9(11)-dehydrohecogenin acetate.

In place of methanol other solvents tried were ethanol, propan-2-ol, diethylene glycol (at 110—120°), and acetone (all mixed with water) but they were no more satisfactory : the products all contained appreciable quantities of Girard-reactive material and some of them were badly discoloured. Excellent results, however, attended the use of dioxan or *tert.*-butyl alcohol. With either of these (used in a two-phase system with aqueous sodium hydroxide) the crude products contained little or no αβ-unsaturated ketone or material extractable by Girard reagent P; and acetylation, with subsequent debromination, then gave the required ketol diacetate (VIII; R = Ac) in about 80% yield, based on dibromohecogenin acetate. Furthermore, the yield of this diacetate (VIII; R = Ac) was little lower when the crude mixture of dibromo-compounds, obtained from hecogenin acetate (I) in acetic acid, benzene or dioxan, was used in place of pure 11α : 23*a*-dibromohecogenin acetate.

Certain other esters (VIII) were prepared in connection with the experiments described in the next paper; the dibenzoate, dimethanesulphonate, and di*iso*butyrate were obtained by standard methods. However, only the 3-monopivalate could be obtained, presumably because of steric hindrance in ring C. The 3-monoacetate was prepared by treatment of the diol (VIII; R = H) with acetic acid and acetic anhydride (cf. ref. 4) and was converted into the 3-acetate 12-methanesulphonate.

Since the treatment of dibromohecogenin acetate with alkali might lead not only to the desired 12β-hydroxy-11-ketone, but also to other isomeric 11 : 12-ketols, it seemed desirable to have these ketols for reference, and methods for their preparation have been investigated.

The 11β-hydroxy-12-ketone was obtained as its 23*a*-bromo-derivative (IX) by gentle hydrolysis of 11α : 23*a*-dibromohecogenin acetate (VI) or the corresponding free alcohol with ethanolic sodium hydroxide. Girard separation served to remove the unreactive 12β-hydroxy-11-ketone and, after acetylation, the monoacetate (IX; R = H) was obtained



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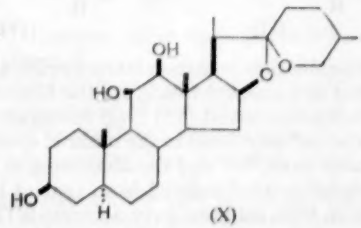


(X)

in poor yield. The reactivity of the ketone group to ketonic reagents proved it to be at position 12 rather than 11, and the β-configuration of the 11-hydroxy-group was shown by reduction with lithium aluminium hydride and subsequent debromination by zinc, which converted the ketol into 5α : 25*D*-spirostan-3β : 11β : 12β-triol (X).[16] In addition to the monoacetate (IX; R = H), the 3β : 11β-diacetoxy-12-ketone (IX; R = Ac) was isolated in small yield. Its structure was shown both by its slow formation from the monoacetate (IX; R = H) by acetic anhydride and pyridine at room temperature and by its reduction to the 3β : 11β : 12β-triol (X). The acetylation of the 11β-hydroxy-group under

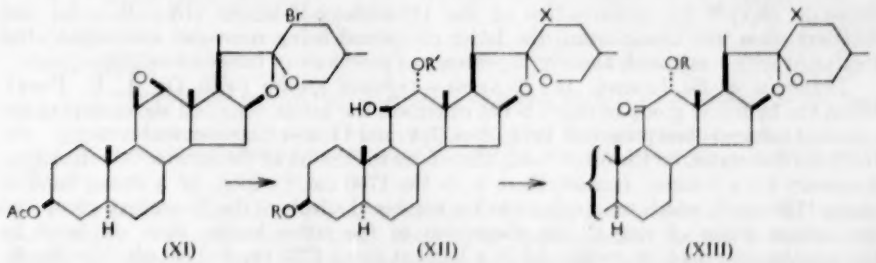
[16] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278.

mild conditions may be associated with the presence of the 12-oxo-group; there are reports of the acetylation of isolated 11β-hydroxy-groups by acetic anhydride and pyridine,[17,18] but this reaction is probably slower even than that of our ketol.

Attempts to debrominate the spirostans (IX; R = H and Ac) with zinc in acetic acid were complicated by other changes. The former underwent rearrangement to yield 3β-acetoxy-12β-hydroxy-5α : 25*D*-spirostan-11-one (IV; R = Ac, X = H) (see below), whereas the latter lost its 11β-acetoxy-group as well as the bromine atom and gave hecogenin acetate (I).

Mueller *et al.*[10] prepared the free diol corresponding to (IX) by a method similar to ours and claimed also to have prepared 3β-acetoxy-11β-hydroxy-5α : 25*D*-spirostan-12-one (IX; R = H; H in place of Br) by alkaline hydrolysis of dibromohecogenin acetate, with subsequent perchloric acid-catalysed acetylation (without intermediate purification) and debromination with zinc in acetic acid. In view of our observations on the comparative ease of acetylation of the 11β-hydroxy-group in the monoester (IX; R = H) and also on the reactions of it and the diacetate with zinc and acetic acid, this reputed isolation of the 11β-hydroxy-12-ketone is rather surprising. Rosenfeld and Gallagher [19] recently described an experiment, similar to that of Mueller *et al.*, which yielded hecogenin acetate and, if the conditions of debromination were mild, a compound they believed to be a 3β : 11-diacetoxy-5α : 25*D*-spirostan-12-one. This is in accord with our experiments described above; the diacetoxy-compound can be assigned the 3β : 11β-structure (IX; R = Ac; H in place of Br) by analogy with our 23-bromo-derivative, by the difference of its rotation (+39°) from that of the 11α-epimer (XV) (−42°),[20] and by the similarity of its rotation to that of the diacetate (IX; R = Ac) (+32°) (bromination at $C_{(23)}$ has a small, irregular effect on rotation).

For the preparation of 3β : 12α-diacetoxy-5α : 25*D*-spirostan-11-one (XIII; R = Ac, X = H) and its 23*a*-bromo-derivative (XIII; R = Ac, X = Br), 3β-acetoxy-23*a*-bromo-11β : 12β-epoxy-5α : 25*D*-spirostan (XI) [2,3] was first treated with trichloroacetic acid.[21] The non-crystalline product is believed to have been essentially the 11β-hydroxy-12α-trichloroacetoxy-compound (XII; R = Ac, R′ = CCl_3·CO, X = Br) in view of the analogous

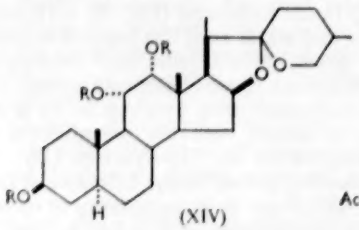


opening of 11β : 12β-epoxides with hydrogen halides to the 11β-hydroxy-12α-halogeno-compounds.[2,3,21] Alkaline hydrolysis of the trichloroacetate gave 23*a*-bromo-5α : 25*D*-spirostan-3β : 11β : 12α-triol (XII; R = R′ = H, X = Br), which was debrominated by zinc and acetic acid to the halogen-free triol (XII; R = R′ = X = H). The triols gave only diacetates under normal acetylating conditions, and these are assigned the structures (XII; R = R′ = Ac, X = Br and H, respectively). Finally, oxidation of the triol diacetates with the chromic anhydride–pyridine complex gave the required 12α-acetoxy-11-ketones (XIII; R = Ac, X = Br and H, respectively). The former was converted into the latter by treatment with zinc in acetic acid. Baumgartner and Tamm [22] recently

[17] Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817.
[18] Kemp, Kappas, Salamon, Herling, and Gallagher, *J. Biol. Chem.*, 1954, **210**, 123.
[19] Rosenfeld and Gallagher, *J. Amer. Chem. Soc.*, 1955, **77**, 4367.
[20] Wendler, Hirschmann, Slates, and Walker, *ibid.*, p. 1632.
[21] Cf. Fürst and Scotoni, *Helv. Chim. Acta*, 1953, **36**, 1410.
[22] Baumgartner and Tamm, *ibid.*, 1955, **38**, 441.

described the preparation of methyl 3α : 12α-diacetoxy-11-oxocholanoate by a method analogous to that described above for the preparation of (XIII). By using acetic acid rather than trichloroacetic acid, they obtained the intermediate triol diacetate directly, but their yield was poor.

The structures assigned to the 12α-hydroxy-compounds were confirmed as follows : the 5α : 25*D*-spirostan-3β : 11 : 12-triol, prepared by the action of osmium tetroxide on the Δ^{11}-olefin,[23] readily formed a triacetate and must, therefore, be the 3β : 11α : 12α-triol (XIV; R = H). The structures of the 3β : 11α : 12β-triol and the 3β : 11β : 12β-triol have been convincingly demonstrated by Wendler *et al.*[20] As our triol, prepared from the 3β-hydroxy-11β : 12β-epoxide, differs from these three, it must, by exclusion, be the 3β : 11β : 12α-triol. The paper-chromatographic behaviour of the isomeric triols is to be discussed in a later Part of this series.[24]



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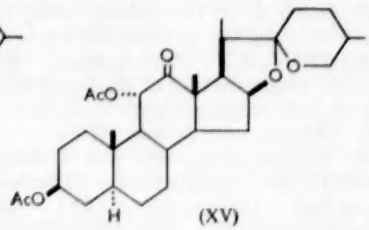

(XV)

The structure of our 12α-hydroxy-11-ketone (XIII; R = X = H) appears to be soundly based on the method of preparation, but additional evidence is derived from (*a*) the reduction of the diacetate (XIII; R = Ac, X = H) to 11-oxotigogenin, indicating the presence of an 11-oxo-group (see next paper), and (*b*) its non-identity with the 12β-hydroxy-11-ketone (VIII), the structure of which has been proved by Wendler *et al.*[20]

An attempt to obtain the remaining ketol, *i.e.*, the 11α-hydroxy-12-ketone, as its diacetate (XV)[20] by epimerisation of the 11β-acetoxy-12-ketone (IX; R = Ac) and debromination was unsuccessful, the latter compound being recovered unchanged after treatment with acetic acid, alone or in presence of perchloric or toluene-*p*-sulphonic acid.

Properties of the Isomeric 11 : 12-*Ketols.—Infrared spectra* (with Dr. J. E. Page). When the hydroxyl group in ring C is not esterified, the ketols described above display the expected infrared absorption (see Table, Nos. 7, 9, and 11, also Experimental section). For the ketol diacetates, on the other hand, there is no maximum at the normal C=O stretching frequency for a ketone; instead, there is, in the 1700 cm.$^{-1}$ region, (*a*) a strong band at about 1730 cm.$^{-1}$, which we attribute to the combined effects of the 3β-acetoxy-group and the ketone group of ring C, the absorption of the latter having been displaced by the neighbouring acetoxy-group, and (*b*) a band at about 1750 cm.$^{-1}$ (1740 cm.$^{-1}$ for No. 6), which can be attributed to the acetoxy-group of ring C, the absorption having been displaced from the normal C=O stretching frequency by the neighbouring keto-group. Bands at about 1240 and 1220 cm.$^{-1}$ are, again, attributed to normal and displaced acetate absorption (C–O stretching)[13,25] (Table, Nos. 6, 8, 10, 12).

These results, which are in general agreement with those quoted by Jones and Herling[26] for 11 : 12-ketol derivatives, invite comparison with the spectra of steroid α-bromo-ketones. The absorption due to a ketone group is displaced to higher frequencies by an equatorial, but not by an axial, bromine atom attached to the neighbouring carbon atom;[13,14] it appears, however, that an acetoxy-group can cause a similar displacement irrespective of its configuration. Nevertheless, the literature does not suggest that this is a regular phenomenon : there appears to be but little mutual interaction between a 20-oxo- and a

[23] Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013.
[24] Brooks, Hunt, Long, and Mooney, *J.*, in the press.
[25] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820.
[26] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.

17-acetoxy-group in either of the possible configurations,[25,26,27] whereas in the 17*a*-acetoxy-17-oxo-D-homosteroids the equatorial 17*a*β-epimer shows a considerable displacement of both ketone and acetoxy-absorption (max. at 1729 and 1756 cm.$^{-1}$ respectively) in contrast to the axial 17*a*α-epimer (max. at 1716 and 1737 cm.$^{-1}$ respectively).[26]

Jones *et al.*[14,25] suggest that a field effect is responsible for the displacements observed in both the bromo- and the acetoxy-ketones and that with the former it operates only when

Physical properties of some of the 11 : 12-*ketols and their derivatives.**

No.	Compound	Infrared absorption † $\nu_{max.}$ (1700 region) (cm.$^{-1}$)	Infrared absorption † $\nu_{max.}$ (1200 region) (cm.$^{-1}$)	Ultraviolet absorption in EtOH $\lambda_{max.}$ (mμ)	log ε	$[M]_D$
1	11-Oxotigogenin	1706	—	295—303	1·40	−133°
2	11-Oxotigogenin acetate (II)	1708, 1730	1240	298—304	1·38	−184
3	Hecogenin	1710	—	284—290	1·65	+30
4	Hecogenin acetate (I)	1706, 1732	1238	287	1·58	−12
5	23*a*-Bromohecogenin acetate	1712, 1736	1240	288	1·63	−77
6	3β : 11α-Diacetoxy-5α : 25*D*-spirostan-12-one (XV)	1729, 1740	—	—	—	−224
7	3β-Acetoxy-23*a*-bromo-11β-hydroxy-5α : 25*D*-spirostan-12-one (IX; R = H)	1705, 1732	1240	307	1·65	+17
8	3β : 11β-Diacetoxy-23*a*-bromo-5α : 25*D*-spirostan-12-one (IX; R = Ac)	1720, 1735, 1750	1218, 1238	303—306	1·90	+195
9	3β : 12α-Dihydroxy-5α : 25*D*-spirostan-11-one (XIII; R = X = H)	1703	—	306—320	1·75	−59
10	3β : 12α-Diacetoxy-5α : 25*D*-spirostan-11-one (XIII; R = Ac, X = H)	1735, 1756	1220, 1238	310	1·84	+28
11	3β : 12β-Dihydroxy-5α : 25*D*-spirostan-11-one (VIII; R = H)	1708	—	290	1·56	−185
12	3β : 12β-Diacetoxy-5α : 25*D*-spirostan-11-one (VIII; R = Ac)	1730, 1750	1230, 1236	293	1·47	−421

Group	Conformation	Differences $\Delta\lambda_{max.}$ (mμ) ‡	ΔM ‡
12β-Hydroxy	e	−9 (−12)	−50° (+77°)
11α-Acetoxy	e	—	−212 (−282)
12β-Acetoxy	e	−8 (−5)	−237 (−24)
11β-Hydroxy	a	+19 (+15 to +23)	+94 (+63)
12α-Hydroxy	a	+14	+74 (+36)
11β-Acetoxy	a	+16 (+7 to +11)	+272 (+158)
12α-Acetoxy	a	+9	+212 (+322)

* All determinations made in these laboratories except for No. 6, in which instance the figures are taken from ref. 20.

† All measurements made in CS_2, except for item 9, where chloroform was the solvent.

‡ Figures in parentheses are corresponding values for the cholanic acid series. For references see text.

the C–Br bond is roughly coplanar with the C=O bond (as in the equatorial bromo-compounds). In the acetoxy-ketones, the relative dispositions of the two C=O bonds are not fixed in this way, and this may account for the decidedly less regular effects upon the infrared absorption.

Ester groupings other than acetate can also cause a displacement of the C=O stretching frequency of a neighbouring ketone group. Thus, in the esters of 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one, a 12β-methanesulphonyloxy- or 12β-*iso*butyryloxy-group causes the ketone band to appear at about 1730 cm.$^{-1}$; a benzoyloxy-group has a smaller effect, the ketone band occurring at 1718 cm.$^{-1}$. Although in the last two instances the reciprocal effect can be observed in the displacement of the C=O stretching frequency of the ester groupings (to 1746 and 1730 cm.$^{-1}$ respectively), it is less clear whether the same is true of the C–O stretching frequency in these esters.

The spectra of the di*iso*butyrate (VIII; R = Pr^{i}·CO), the 3-monopivalate (IV; R = Bu^{t}·CO, X = H), and the dibenzoate (VIII; R = Bz) showed C–O stretching bands at positions agreeing with those found by Thompson and Torkington in simple alkyl esters [28] and with those found by us in the corresponding *cyclo*hexyl esters.

[27] Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489.
[28] Thompson and Torkington, *J.*, 1945, 640.

Again, the 3-acetate 12-methanesulphonate and the 3 : 12-dimethanesulphonate of the ketol (VIII; R = H) absorbed within the ranges suggested by Colthup [29] for a covalent sulphonate group.

Ultraviolet spectra. Studies of the 11 : 12-ketols in the cholanic acid series have shown that the position of the weak ketone band is displaced by a neighbouring hydroxy- or acetoxy-group, the direction of the shift depending on the conformation of the substituent.[22,30,31] In this respect, such groups resemble similarly placed bromine atoms.[30,32]

It will be seen from the Table that for the sapogenin 11 : 12-ketols and their acetates there are displacements of the ketone band very similar to those observed for the cholanic acid analogues.

Rotations. The Table shows the molecular-rotation contributions of 11- and 12-hydroxy- and -acetoxy-groups in the 11 : 12-ketols. Though the individual values differ considerably from those derived by Baumgartner and Tamm [22] from the 11 : 12-ketols in the cholanic series (and variations in their solvents may account for part of the difference [33]), a similar pattern can be discerned. In particular, in both series an axial acetoxy-group makes a strongly positive contribution to the molecular rotation, whereas an equatorial acetoxy-group has the opposite effect (though, in the cholanic series, the ΔM value for a 12β-acetoxy-group is only −24°). Again, in both series, acetylation of an axial hydroxy-group changes the ΔM value in a positive sense, whereas acetylation of an equatorial hydroxy-group results in a negative change of molecular rotation.

Paper chromatography. This will be discussed in a later Part of this series.[24]

Interconversion of the ketols. The formation of a 12β-hydroxy-11-ketone from an 11-bromo-12-ketone under the action of alkali involves initial hydrolysis, with inversion, to an 11-hydroxy-12-ketone, and subsequent rearrangement, presumably through an 11-ene-11 : 12-diol or an ionised form thereof.[10,19,34] Ketonisation of the enediol might give rise to any of the four isomeric ketols, and the proportions in which they occur in the equilibrium mixture will depend on their relative stabilities under the conditions employed.

The preparation of the diacetate (VIII; R = Ac) from dibromohecogenin acetate in 80% yield suggests that the equilibrium mixture in this series consists almost entirely of the 12β-hydroxy-11-ketone. This is borne out by the published statement that the bromo-ketol (VII; R = H) is unaffected by vigorous treatment with caustic alkali,[10] as well as by our own experiments on the stability of the debrominated ketol (VIII; R = H) to alkali.

Both the 11β-hydroxy-12-ketone (IX; R = H) and the 11β-acetoxy-12-ketone (IX; R = Ac) were readily rearranged to 23*a*-bromo-3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (VII; R = H) by a boiling solution of sodium hydroxide in aqueous *tert.*-butyl alcohol. The monoacetate was also rearranged slowly by caustic alkali at room temperature and quickly by boiling methanolic hydrochloric acid. More surprising was the observation that the 11β-hydroxy-12-ketone (IX; R = H) was converted into 3β-acetoxy-23*a*-bromo-12β-hydroxy-5α : 25*D*-spirostan-11-one (IV; R = Ac, X = Br) by acetic acid at 100°; this unexpectedly easy rearrangement explained the conversion of the former compound (IX; R = H) into the 12-hydroxy-11-ketone (IV; R = Ac, X = H) under the action of zinc and acetic acid (see above).

The 12α-hydroxy-11-ketones (XIII) were far more stable to both acid and alkaline conditions than were the 11β-hydroxy-12-ketones. The diacetate (XIII; R = Ac, X = H), for example, was merely hydrolysed to the corresponding diol by a boiling solution of sodium hydroxide in aqueous *tert.*-butyl alcohol (this is discussed further below). On more vigorous treatment with alkali, the ketol was epimerised to the 12β-hydroxy-11-ketone (VIII; R = H), but it was unaffected by prolonged boiling with 2N-alcoholic hydrochloric acid.

[29] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.
[30] Cookson and Dandegaonker, *J.*, 1955, 352.
[31] Schindler and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 667.
[32] Cookson, *J.*, 1954, 282.
[33] Cf. Norymberski, *J.*, 1954, 762.
[34] Gallagher and Long, *J. Biol. Chem.*, 1946, **162**, 521; Gallagher and Hollander, *ibid.*, p. 533; Gallagher, *ibid.*, p. 539.

Finally, it should be mentioned that Wendler *et al.*[20] have reported that the 11α-acetoxy-12-ketone (XV) is converted quantitatively into the 12β-hydroxy-11-ketone (VIII; R = H) by boiling 2N-methanolic potassium hydroxide.

The ease of rearrangement of the 11β-hydroxy-12-ketone compared with that of the 12α-hydroxy-11-ketone stands in contrast with the enol acetylation of 11-oxo-steroids under conditions that have no effect upon 12-oxo-compounds.[35,36] However, enol acetylation of an 11-ketone, unsubstituted at position 12, gives the 11-acetoxy-$\Delta^{9(11)}$-compound;[7b,36,37] if this is also the preferred direction of enolisation in the ketol (XIII), the sluggishness of the epimerisation may be explained.

Reference has been made above to the stability of the 12α-hydroxy-11-ketone (XIII; R = X = H) under the alkaline conditions that convert dibromohecogenin acetate into the 12β-hydroxy-11-ketone. This implies that the bromo-compound (XIII; R = H, X = Br) is not an intermediate in this reaction and, hence, that the kinetically as well as the thermodynamically controlled protonation of the common enediol at $C_{(12)}$ occurs entirely, or nearly so, in the axial α-position. Corey [38] has recently advanced the theory that in the kinetically controlled ketonisation of an enolised *cyclo*hexanone, the incoming substituent adopts the axial configuration preferentially; the theory was supported by much experimental evidence drawn from bromination of ketones, but none was offered to support the belief that the rule applies also to protonation of enols. Our findings now provide one piece of experimental evidence to support this aspect of Corey's theory.

The formation in this series of the 12β-hydroxy-11-ketone as virtually the sole product of the action of alkali on the isomeric ketols is different from the situation in the cholanic acid series, in which the 12β-hydroxy-11-ketone, 11α-hydroxy-12-ketone, 12α-hydroxy-11-ketone, and 11β-hydroxy-12-ketone were isolated in yields of 63·1, 30·4, 1·1%, and "a trace," respectively.[8] The difference cannot be a result of the different configurations at $C_{(5)}$, or of the presence of an acidic side chain in only one of the series of compounds, since Gallagher [39] has shown that 3α : 12β-dihydroxy-11-oxoetianic acid is stable to alkali. The factors influencing the relative stabilities of the 12-hydroxy-11-ketones and 11-hydroxy-12-ketones remain obscure, although the nature of the side chain is clearly important. There is, indeed, other evidence that reactions at $C_{(11)}$ and $C_{(12)}$ in the spirostan and the etianic acid series are similar, and that they differ from those in the cholanic acid series, and this has been attributed to the steric effect of the long, freely rotating cholanic acid side chain.[10]

Experimental

For general experimental information, see Part XIII.

11α : 23a-*Dibromohecogenin Acetate* (VI).—A suspension of hecogenin acetate (100 g.) in dry benzene (150 ml.) was treated with a few ml. of a 4·0N-solution of bromine in benzene. When the colour had been discharged, the remainder of the bromine solution (245 ml. in all) was added during 10 min. with continual swirling. During this time, the hecogenin acetate dissolved, an orange solid (probably a complex of hecogenin acetate with bromine) separated, and this, in turn, went into solution. The solvent was then removed rapidly under reduced pressure at room temperature and the residual gum was dissolved in boiling ethanol (1 l.) (swirling is necessary to effect rapid dissolution); 11α : 23a-dibromohecogenin acetate separated almost immediately and after the mixture had cooled to room temperature the solid was filtered off, washed with a little cold ethanol, and dried. The product (70·6 g., 53%) had m. p. 180—182° (decomp.) and $[\alpha]_D$ −38°. For infrared spectrum see ref. 13. Reported m. p.s of this compound vary between 180—183° (decomp.) and 189—191° (decomp.); the rotation is given as −38° and −39·3°.[5,5,15]

The mother-liquors from the crystallisation were added, without undue delay, to a zinc–copper couple, which had been freshly prepared from zinc dust (200 g.) and copper sulphate solution (15% w/v; 1350 ml.) and washed with ethanol. The mixture was boiled under reflux with stirring for 3 hr., and filtered while hot. The solid residue was washed with methylene

[35] Hirschmann, Brown, and Wendler, *J. Amer. Chem. Soc.*, 1951, **73**, 5373.
[36] Hirschmann and Wendler, *ibid.*, 1953, **75**, 2361.
[37] Crawshaw, Henbest, and Jones, *J.*, 1954, 731.
[38] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.
[39] Gallagher, *J. Biol. Chem.*, 1946, **165**, 211.

chloride, and the combined filtrate and washings were concentrated under reduced pressure to *ca.* 500 ml. Water and 2N-hydrochloric acid (50 ml.) were added and the crude hecogenin acetate was filtered off, washed with water, and dried. Crystallisation from chloroform–methanol gave material (32 g.) suitable for rebromination.

11α : 23a-*Dibromohecogenin*.—A solution of the acetate (5·0 g.) in benzene (75 ml.) and methanol (500 ml.) was treated with concentrated hydrochloric acid (5 ml.) and the solution was left at room temperature for 24 hr. The solvents were removed under reduced pressure and the residue was dissolved in a little methanol. 11α : 23a-*Dibromohecogenin* (3·63 g.) gradually separated as needles that decomposed between 181° and 189° and had $[\alpha]_D$ −34°; a second crop weighed 0·40 g. (total yield 86%) and had similar constants. Further crystallisation from methanol gave material, decomp. *ca.* 180°, $[\alpha]_D$ −33° (Found : C, 55·1; H, 6·7. $C_{27}H_{40}O_4Br_2$ requires C, 55·1; H, 6·85%). Infrared spectrum : see ref. 13.

Bromination of Hecogenin Acetate in Carbon Tetrachloride.—A solution of hecogenin acetate (30 g.) in carbon tetrachloride (600 ml.) was stirred while bromine (6·75 ml.) in carbon tetrachloride (50 ml.) was added during 15 min. After a further 15 min., the solvent was removed under reduced pressure and 11α : 23*a*-dibromohecogenin acetate (19·5 g., 49%) isolated as described in the previous experiment.

The ethanol mother-liquors were evaporated to dryness under reduced pressure and the residual gum was chromatographed in 3 : 2 benzene–light petroleum on acid-washed alumina (400 g.; Peter Spence, Grade H). Benzene–light petroleum (1 : 1) eluted crude 11α : 23b-*dibromohecogenin acetate* (6·4 g.) which, crystallised first from methanol, then from 3 : 1 methanol–ethyl acetate, gave needles (4 g., 10%), m. p. 168—169° (decomp.) (depressed on admixture with 11α : 23*a*-dibromohecogenin acetate), $[\alpha]_D$ −46° (Found : C, 55·2; H, 6·9; Br, 24·8. $C_{29}H_{42}O_5Br_2$ requires C, 55·3; H, 6·7; Br, 25·35%). Infrared spectrum : see ref. 13. Treatment of the dibromo-compound (0·5 g.) with zinc dust (2·5 g.) in boiling acetic acid (20 ml.) for 2 hr. gave hecogenin acetate (310 mg., 83%), m. p. 243—251°. Its identity was confirmed by infrared spectroscopy.

3β-*Acetoxy*-23b-*bromo*-5α : 25D-*spirost*-9(11)-*en*-12-*one*.—11α : 23*b*-Dibromohecogenin acetate (0·5 g.) in collidine (7 ml.) was boiled under reflux for 1 hr. After being cooled, the solution was diluted with ether, and the precipitated collidine hydrobromide was filtered off. The filtrate was washed with 2N-hydrochloric acid and water, dried, and evaporated. Crystallisation of the residue from ethanol gave the unsaturated ketone as prisms (0·29 g., 67%), m. p. 219—220° (decomp.), $[\alpha]_D$ −47° (in $CHCl_3$), −48° (in dioxan) (Found : Br, 14·2. Calc. for $C_{29}H_{41}O_5Br$: Br, 14·5%), $\lambda_{max.}$ 237·5 mμ (ε 12,700). Infrared spectrum : see ref. 13. Mueller and Norton [15] give m. p. 220—221° (decomp.), $[\alpha]_D$ −47·2° (in dioxan), $\lambda_{max.}$ 238 mμ (ε 13,800).

3β : 12β-*Diacetoxy*-5α : 25D-*spirostan*-11-*one* (VIII; R = Ac).—(a) *From* 11α : 23a-*dibromohecogenin acetate*. The dibromo-compound (50 g.) was boiled under reflux for 6 hr. with a stirred solution of sodium hydroxide (25 g.) in *tert.*-butyl alcohol (500 ml.) and water (500 ml.); the mixture was a two-phase one throughout. Removal of the alcohol by distillation under reduced pressure, dilution of the residue with water to 2 l., and filtration gave the crude crystalline 23-bromo-ketol (VII; R = H) (42·0 g.); treatment with Girard reagent P extracted about 2% of this material. The crude bromo-ketol was boiled under reflux for 1 hr. with pyridine (375 ml.) and acetic anhydride (375 ml.). The solution was evaporated to dryness *in vacuo* and the residue was evaporated with methanol. Debromination of the residue by stirring it with zinc dust (170 g.) in boiling acetic acid (450 ml.) for 2 hr., filtration, and dilution with water gave a crude product (40·5 g.) which, on crystallisation from ethanol, yielded in two crops, 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one (34·1 g., 81%), m. p. 222—225°, $[\alpha]_D$ −78°.

(b) *From hecogenin acetate* via *the crude dibromo-derivative*. A solution of hecogenin acetate (25·0 g.) in dry benzene (200 ml.) was stirred during the addition of bromine (6·2 ml.) in benzene (50 ml.); after the first few ml. had been decolorized, the remainder was added in 5 min. The solution was left for a further 10 min. and was then concentrated *in vacuo* at <20° to about 40 ml. Sodium hydroxide solution (5%; 250 ml.) and *tert.*-butyl alcohol (300 ml.) were added and distillation was continued, with stirring, to remove the residual benzene. Hydrolysis, acetylation, and debromination as in (*a*) gave a first crop (19·8 g., 71%) of the required ketol diacetate, m. p. 224—227°, $[\alpha]_D$ −79°, and, by fractional crystallisation of the residue from ethanol, a further 1·63 g. (6%) of material with similar constants.

A similar yield of 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one was obtained when hecogenin acetate was brominated by the method of Djerassi *et al.*[11] and the crude dibromo-compound treated as above. Again, dioxan could be used for both the bromination and the hydrolysis stage as follows : Hecogenin acetate (25 g.) in dioxan (250 ml.) was treated with bromine

(6·0 ml.) and after being stirred at room temperature for 40 min., the solution was treated with sodium hydroxide (25·0 g.) in water (250 ml.) and boiled under reflux for 6 hr. The crude bromo-ketol so obtained was acetylated and debrominated as described above, to give a first crop of 19·6 g. (70%) of the ketol diacetate.

A sample of 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one, crystallised to constant m. p. from ethanol and from benzene–light petroleum, had m. p. 223—226°, $[\alpha]_D$ −79·5° (*c* 2), $[\alpha]_D$ −72° (*c* 3 in dioxan), $\nu_{max.}$ (in CS_2) 1750 and 1230 (displaced OAc), 1730 (displaced CO), 1730 and 1236 (OAc), 978, 916, and 896 cm.$^{-1}$ (25*D*-spirostan). Djerassi *et al.*[11] give m. p. 225—225·5°, $[\alpha]_D$ −67° ($CHCl_3$); Mueller *et al.*[10] give $[\alpha]_D$ −71·8° (dioxan).

3β : 12β-*Diacetoxy*-23a-*bromo*-5α : 25D-*spirostan*-11-*one* (VII; R = Ac).—11α : 23a-Dibromohecogenin acetate (50 g.) was treated with alkali as described in experiment (*a*) above and the crude bromo-ketol (38·4 g.) obtained after treatment with Girard reagent was acetylated for 2 hr. with acetic anhydride (60 ml.) and pyridine (60 ml.) at the b. p. The acetylating mixture was removed under reduced pressure and the residue dissolved in acetic acid (300 ml.). Dilution with water (3 l.) gave a solid that melted at 196° after crystallisation from methanol (yield 28·8 g., 60%). After further crystallisation from the same solvent, the *ketol diacetate* had m. p. 196—198°, $[\alpha]_D$ −66° (Found: C, 61·4; H, 7·4; Br, 13·0. $C_{31}H_{45}O_7Br$ requires C, 61·1; H, 7·4; Br, 13·1%). Infrared spectrum: see ref. 13.

Debromination of this compound with zinc in boiling acetic acid gave a 92% yield of 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one (VIII; R = Ac).

Hydrolysis of the bromo-ketol diacetate with a boiling 3% solution of potassium hydroxide in 85% aqueous methanol for 1 hr. gave 23*a*-bromo-3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (VII; R = H), crystallising from aqueous methanol in needles, which melted at 135°, resolidified, and melted finally at 208—210°, $[\alpha]_D$ −33° (in $CHCl_3$), −29° (*c* 1 in dioxan). For analysis it was dried at 120°/0·05 mm. (Found: C, 61·4; H, 7·8; Br, 14·9. Calc. for $C_{27}H_{41}O_5Br$: C, 61·7; H, 7·9; Br, 15·2%). Infrared spectrum: ref. 13. Mueller *et al.*[10] give m. p. 233—234° (decomp.), $[\alpha]_D$ −23·7° (dioxan).

3β-*Acetoxy*-23a-*bromo*-12β-*hydroxy*-5α : 25D-*spirostan*-11-*one* (IV; R = Ac, X = Br).—A mixture of 23*a*-bromo-3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (5·0 g.), acetic acid (50 ml.), and acetic anhydride (5·0 ml.) was boiled for 1 hr.; water (25 ml.) was added and the mixture refluxed for a further 30 min. Water (*ca.* 200 ml.) was gradually added to the hot mixture and, after cooling, the solid was filtered off. Crystallisation from aqueous ethanol (charcoal) gave the *monoacetate* (3·7 g., 69%) as needles, m. p. 214° (decomp.), $[\alpha]_D$ −41·0° (*c* 1·3) (Found: C, 61·7; H, 7·6; Br, 13·9. $C_{29}H_{43}O_6Br$ requires C, 61·4; H, 7·65; Br, 14·1%), $\nu_{max.}$ (in CS_2) 3500 (OH), 1734 and 1240 (OAc), 1710 (CO), 1010, 945, 918, and 726 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

3β : 12β-*Dihydroxy*-5α : 25D-*spirostan*-11-*one and Various Esters thereof.*—*Diol* (VIII; R = H). This was prepared by hydrolysis of the diacetate with a boiling 3% solution of sodium hydroxide in 90% aqueous methanol for 3 hr. It separated from aqueous methanol or aqueous acetone as a hydrate, m. p. 212—214°, $[\alpha]_D$ −40° (*c* 1 in $CHCl_3$), −39° (*c* 1·5 in dioxan). The hydrate lost its water at 120° in a high vacuum. The diol had infrared max. (in CS_2) at 3620 and 3500 (OH), 1708 (CO), 976, 916, and 896 cm.$^{-1}$ (25*D*-spirostan). Mueller *et al.*[10] give m. p. 217—218°, $[\alpha]_D$ −40° (dioxan). The rotation (−13° in $CHCl_3$) given by Djerassi *et al.*[11] is presumably incorrect.

3-*Monoacetate* (IV; R = Ac, X = H). The ketol hydrate (20·0 g.) was boiled for 1 hr. with acetic acid (200 ml.) and acetic anhydride (20 ml.). Water (200 ml.) was gradually added to the boiling solution and, after cooling, the mixture was further diluted with water to *ca.* 1 l. and filtered. Crystallisation of the solid from methanol gave the 3-monoacetate (11·6 g., 55%) as prisms, m. p. 214—218°, $[\alpha]_D$ −48° (*c* 1) (Found: C, 71·5; H, 9·2. Calc. for $C_{29}H_{44}O_6$: C, 71·3; H, 9·1%), $\nu_{max.}$ (in CS_2) 3500 (OH), 1733 and 1236 (OAc), 1708 (CO), 976, 916, and 896 cm.$^{-1}$ (25*D*-spirostan). Djerassi *et al.*[4] give m. p. 212—215°, $[\alpha]_D$ −30°.

3-*Acetate* 12-*methanesulphonate*. The 3-monoacetate (12 g.) in pyridine (70 ml.) was cooled in ice while methanesulphonyl chloride (7 ml.) was added dropwise. After being kept overnight at room temperature, the solution was poured on ice, and the precipitate extracted with benzene. The extract was washed with 2N-hydrochloric acid and water, then evaporated to dryness, and the residue crystallised from methanol. 3β-*Acetoxy*-12β-*methanesulphonyloxy*-5α : 25D-*spirostan*-11-*one* (12·6 g., 90%) had m. p. 173—175°, raised by further crystallisation to 174—176°, $[\alpha]_D$ −64° (*c* 1) (Found: C, 63·8; H, 8·3. $C_{30}H_{46}O_8S$ requires C, 63·6; H, 8·2%), $\nu_{max.}$ (in CS_2) 1730 and 1240 (OAc), 1730 (displaced CO), 1360 and 1175 (methanesulphonate), 976, 917, and 895 cm.$^{-1}$ (25*D*-spirostan). The same compound could be prepared in 90% overall

yield from the free ketol by monoacetylation as above, followed by methanesulphonylation of the uncrystallised monoacetate.

3-*Monopivalate* (IV; R = Bu^t·CO, X = H). Treatment of the ketol (4·0 g.) in pyridine (20 ml.) with pivalyl chloride (4 ml.) overnight at room temperature, isolation with ether, and crystallisation from ethanol gave the 3-*monopivalate* (3·6 g., 77%), m. p. 229—237°. After crystallisation from acetone, it had m. p. 232—236°, $[\alpha]_D$ −41° (Found: C, 72·6; H, 9·6. $C_{32}H_{50}O_4$ requires C, 72·4; H, 9·5%), $\nu_{max.}$ (in CS_2) 3500 (OH), 1723, 1280, 1162, and 1145 (trimethylacetate), 1708 (CO), 980, 920, and 899 cm.$^{-1}$ (25*D*-spirostan).

3 : 12-*Dibenzoate* (VIII; R = Bz). Treatment of the ketol (3·0 g.) with benzoyl chloride (3·0 ml.) in pyridine (40 ml.) overnight at room temperature gave the *dibenzoate*, crystallising from methanol in plates (2·6 g., 61%), m. p. 280—285°, $[\alpha]_D$ −61° (*c* 1) (Found: C, 75·1; H, 7·8. $C_{41}H_{50}O_7$ requires C, 75·2; H, 7·7%), $\nu_{max.}$ (in CS_2) 1730 (displaced benzoate), 1718, 1265, 1112, and 716 (benzoate), 1718 (displaced CO), 980, 918, 898, and 862 cm.$^{-1}$ (25*D*-spirostan).

3 : 12-*Diisobutyrate* (VIII; R = Pr^i·CO). Treatment of the ketol (5·0 g.) with *iso*butyryl chloride (10 ml.) in pyridine (20 ml.) at room temperature for 65 hr., followed by precipitation and crystallisation from ethanol, gave the *diisobutyrate* (3·67 g., 58%), m. p. 192—197°. After further crystallisation it had m. p. 198—202°, $[\alpha]_D$ −65° (*c* 1) (Found: C, 72·1; H, 9·0. $C_{35}H_{54}O_7$ requires C, 71·6; H, 9·3%), $\nu_{max.}$ (in CS_2) 1746 (displaced *iso*butyrate), 1728, 1240, 1188, and 1152 (*iso*butyrate), 1728 (displaced CO), 978, 916, and 896 cm.$^{-1}$ (25*D*-spirostan).

3 : 12-*Dimethanesulphonate* (VIII; R = Me·SO_2). The ketol (1 g.) was treated with methanesulphonyl chloride (2 ml.) in pyridine (10 ml.) overnight at room temperature. Isolation with benzene and crystallisation from benzene–methanol gave the *dimethanesulphonate* (1·12 g., 86%), m. p. 165—166° (decomp.) (Found: S, 10·3. $C_{29}H_{46}O_9S_2$ requires S, 10·6%), $\nu_{max.}$ (in Nujol) 1726 (displaced CO), 1360 and 1175 (methanesulphonate), 978, 918, and 895 cm.$^{-1}$ (25*D*-spirostan).

3β-*Acetoxy*-23a-*bromo*-11β-*hydroxy*-5α : 25D-*spirostan*-12-*one* (IX; R = H).—11α : 23*a*-Dibromohecogenin (2 g.) was dissolved in hot ethanol (320 ml.), the solution was cooled to room temperature, and 40% sodium hydroxide solution (17 ml.) was added. After 30 min., the solution was acidified with a slight excess of acetic acid and evaporated to small bulk under reduced pressure. Dilution of the residue with water gave a solid (1·82 g.), $[\alpha]_D$ −13°. This material (1·78 g.) was boiled under reflux for 1 hr. in ethanol (30 ml.) containing Girard reagent P (1 g.) and acetic acid (3 ml.). The solution was poured into water (200 ml.) containing sodium hydrogen carbonate (5 g.), a trace of solid was filtered off, and the solution was acidified with hydrochloric acid. The precipitated solid (1·68 g.) was acetylated overnight at room temperature with pyridine (10 ml.) and acetic anhydride (10 ml.). The solid obtained by precipitation with water was triturated with methanol and then yielded a microcrystalline solid which, on crystallisation from ethanol, gave the 3-*monoacetate* (0·48 g., 27%), m. p. 201—209° (decomp.), $[\alpha]_D$ +2·7° (*c* 0·5) (Found: C, 61·0; H, 7·6; Br, 14·0. $C_{29}H_{43}O_6Br$ requires C, 61·35; H, 7·6; Br, 14·1%), $\nu_{max.}$ (in Nujol) 3460 (OH), 1710 and 1266 (OAc), 1012, 946, 918, 864, and 726 cm.$^{-1}$ (23a-bromo-25*D*-spirostan). On one occasion, the compound was obtained as prisms, m. p. 218°, $[\alpha]_D$ +3°; crystallisation from acetone or ethanol then gave needles. The infrared spectra of the two crystal forms were distinct in Nujol, that of the prisms being as follows: 1735 and 1240 (OAc), 1705 (CO), 1012, 946, 918, 862, and 726 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan). In bromoform solution, both forms showed identical spectra (see also ref. 40).

The compound gave a precipitate on brief warming in ethanol with Johnson's 2 : 4-dinitrophenylhydrazine–phosphoric acid reagent.[41]

Treatment of the ketol with toluene-*p*-sulphonhydrazide in acetic acid at room temperature gave the *toluene*-p-*sulphonylhydrazone*, m. p. 227—229° (decomp.), $[\alpha]_D$ −32° (*c* 0·99) after crystallisation from chloroform–methanol (Found: C, 58·9; H, 7·4; S, 4·35. $C_{34}H_{51}O_7N_2BrS$ requires C, 58·8; H, 7·0; S, 4·4%), $\nu_{max.}$ in (Nujol) 3620 (OH), 3200 (NH), 1731 and 1255 (OAc), 1350 and 1160 (SO_2·NH), 1007, 952, 920, and 724 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

3β : 11β-*Diacetoxy*-23a-*bromo*-5α : 25D-*spirostan*-12-*one* (IX; R = Ac).—(a) *From* 11α : 23a-*dibromohecogenin acetate*. The dibromo-compound (50 g.) was boiled for 2 hr. with potassium hydroxide (12·5 g.) in 95% methanol (500 ml.). The solution was diluted with water, and the precipitated solid was filtered off. Treatment of this solid with Girard reagent P, as described in the last experiment, yielded 20·9 g. of reactive ketone, which crystallised from methanol as needles (15·0 g.), m. p. 192—195° (decomp.). This crude solid was acetylated for 30 min. on the steam-bath with acetic anhydride (30 ml.) and pyridine (30 ml.). Removal of the

[40] Dickson, Page, and Rogers, *J.*, 1955, 443.
[41] Johnson, *J. Amer. Chem. Soc.*, 1951, **73**, 5888.

excess of acetylating mixture under reduced pressure and trituration of the residue with methanol then gave 3β-acetoxy-23*a*-bromo-11β-hydroxy-5α : 25*D*-spirostan-12-one (8·1 g., 18%) identical with the material described above.

The mother-liquors from the monoacetate were diluted with water, and the solid (8·3 g.), so obtained, was chromatographed on alumina (Peter Spence, Grade O; 200 g.). The material obtained by elution with benzene–light petroleum (3 : 1), benzene, and ether–benzene (1 : 9 and 1 : 4) was crystallised from benzene–light petroleum (b. p. 60—80°), to give 3β : 11β-*diacetoxy*-23a-*bromo*-5α : 25D-*spirostan*-12-*one* (2·8 g., 6%), m. p. 159—169°. Crystallisation from aqueous methanol raised the m. p. to 168—171°; $[\alpha]_D$ was +32° (*c* 1·4) (Found : C, 60·8; H, 7·5; Br, 12·9. $C_{31}H_{45}O_7Br$ requires C, 61·1; H, 7·4; Br, 13·1%), $\nu_{max.}$ (in CS_2) 1750 and 1218 (displaced OAc), 1735 and 1238 (OAc), 1720 (displaced CO), 1010, 945, 920, and 728 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

The *toluene*-p-*sulphonylhydrazone* was prepared as described above for the 3-monoacetate. Crystallised from aqueous acetone, it had m. p. 197—199°, $[\alpha]_D$ −150° (*c* 0·78) (Found : C, 58·9; H, 6·9. $C_{38}H_{53}O_8N_2BrS$ requires C, 58·7; H, 6·9%), $\lambda_{max.}$ (in EtOH) 226·5 mμ (ε = 12,700), $\nu_{max.}$ (in CS_2) 3200 (NH), 1720—1730 and 1238 (OAc), 1165 (SO_2·NH), 1016, 945, 918, and 732 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

(b) *From the 3-monoacetate.* A solution of 3β-acetoxy-23*a*-bromo-11β-hydroxy-5α : 25*D*-spirostan-12-one (200 mg.) in pyridine (2·5 ml.) and acetic anhydride (2·5 ml.) was left at room temperature for 7 days. The solution was poured on ice, and the solid (208 mg.) filtered off; it had $[\alpha]_D$ +27°. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave 109 mg. of the diacetate, m. p. 169—173°, $[\alpha]_D$ +30°.

Lithium Aluminium Hydride Reduction of the 3-Mono- and 3 : 11-Di-acetates of 3β : 11β-Dihydroxy-23a-bromo-5α : 25D-spirostan-12-one.—Reduction of the diacetate (200 mg.) in boiling tetrahydrofuran (5 ml.) with lithium aluminium hydride (100 mg.) and isolation of the product with ether gave a crude product (155 mg.) that was debrominated by treatment with zinc dust (0·7 g.) in boiling acetic acid (5 ml.) for 2 hr. Hydrolysis with boiling 4% methanolic sodium hydroxide for 30 min. then gave a crude product (110 mg.), paper chromatography of which revealed the presence of 5α : 25*D*-spirostan-3β : 11β : 12β-triol but not that of the other 3β : 11 : 12-triols. Crystallisation of the material from aqueous methanol gave the 3β : 11β : 12β-triol (68 mg., 46%) as needles, m. p. 252—257°, $[\alpha]_D$ −66·5°, identified by its infrared spectrum with a sample prepared by the method of Djerassi *et al.*,[16] who give m. p. 262—263°, $[\alpha]_D$ −64°.

A similar reduction of the monoacetate with lithium aluminium hydride left some ketone unchanged, but retreatment with the reducing agent, followed by zinc debromination as described above, gave a crude material in 75% yield that was found, by paper chromatography, to contain 5α : 25*D*-spirostan-3β : 11β : 12β- and -3β : 11β : 12α-triol. Crystallisation from aqueous methanol gave a poor yield of needles, m. p. 248—252°, shown by infrared spectroscopy to consist essentially of the 3β : 11β : 12β-triol.

Action of Zinc upon 3β-Acetoxy-23a-bromo-11β-hydroxy-5α : 25D-spirostan-12-one.—The steroid (100 mg.) was boiled for 2 hr. with zinc dust (100 mg.) and acetic acid (2 ml.). After removal of excess of zinc and zinc salts, dilution with water gave a crude solid (69 mg.) whose infrared spectrum suggested that it consisted largely of 3β-acetoxy-12β-hydroxy-5α : 25*D*-spirostan-11-one (IV; R = Ac, X = H). Acetylation with acetic anhydride (1 ml.) and pyridine (1 ml.) overnight at room temperature and crystallisation from ethanol gave the corresponding diacetate (VIII; R = Ac) (20 mg.), m. p. 225—228°, identified by mixed m. p. and infrared spectrum with an authentic specimen.

Action of Zinc upon 3β : 11β-Diacetoxy-23a-bromo-5α : 25D-spirostan-12-one.—The steroid (200 mg.) was boiled for 4 hr. with zinc dust (2 g.) and acetic acid (6 ml.). The product, isolated as above in 88% yield, was somewhat impure hecogenin acetate, m. p. 225—239°, $[\alpha]_D$ −2·5°. Crystallisation from methanol gave the pure material, m. p. 242—246°.

Rearrangement of the Acetates of 23a-Bromo-3β : 11β-dihydroxy-5α : 25D-spirostan-12-one.—(a) *With sodium hydroxide in aqueous tert.-butyl alcohol.* The 3-monoacetate (200 mg.) was boiled for 6 hr. with 5% aqueous sodium hydroxide (5 ml.) and *tert.*-butyl alcohol (5 ml.). On removal of the alcohol by distillation, 23*a*-bromo-3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (174 mg., 94%) separated {m. p. 214° (decomp.); $[\alpha]_D$ −33° (*c* 0·79)}. Treatment of 3β : 11β-diacetoxy-23*a*-bromo-5α : 25*D*-spirostan-12-one with alkali under the same conditions gave the 12β-hydroxy-11-ketone (VII; R = H), m. p. 214° (decomp.), $[\alpha]_D$ −33°, in 92% yield.

(b) *With alkali at room temperature.* The 3-monoacetate (250 mg.) was left at room temperature with a mixture of 2·5% aqueous potassium hydroxide (16·7 ml.) and dioxan (33·3 ml.).

The specific rotation of the solution, initially +5°, rose in 1½ hr. to +9° and then fell during *ca.* 70 hr. to a steady value of −28°. The 12β-hydroxy-11-ketone (VII; R = H), isolated in the usual way, had m. p. 210° (decomp.), $[\alpha]_D$ −32°.

(c) *With methanolic hydrochloric acid.* Treatment of the 3-monoacetate (0·5 g.) with boiling concentrated hydrochloric acid (2 ml.) and methanol (50 ml.) for 90 min. gave 0·35 g. of crude 12β-hydroxy-11-ketone (VII; R = H), m. p. 210° (decomp.), $[\alpha]_D$ −32°.

(d) *With acetic acid.* A solution of the monoacetate (100 mg.) in acetic acid (10 ml.) was heated at 100°. The specific rotation was initially +11·0° and fell in 6 hr. to a steady value of −23°. Precipitation with water then gave 80 mg. of 3β-acetoxy-23*a*-bromo-12β-hydroxy-5α : 25*D*-spirostan-11-one, m. p. 213° (decomp.), $[\alpha]_D$ −42° (*c* 0·65), identical with a sample prepared as described above.

23a-*Bromo*-5α : 25D-*spirostan*-3β : 11β : 12α-*triol* (XII; R = R′ = H, X = Br).—Trichloroacetic acid (55 g.) was dissolved in toluene and the solution was dried over calcium chloride for a few hours. The solution was filtered, 3β-acetoxy-23*a*-bromo-11β : 12β-epoxy-5α : 25*D*-spirostan [2] (50 g.) was added and the solution was diluted with toluene to about 1 l., left at room temperature for 3 days, then cooled to 0° and washed with cold sodium hydrogen carbonate solution and with water. The toluene solution was dried ($MgSO_4$) and evaporated to dryness. The residue was a glass, $\nu_{max.}$ (in CS_2) 3610 (OH), 1760 and 1240 (trichloroacetate), 1732 and 1240 (OAc), 1014, 948, 918, and 728 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

The crude trichloroacetate was boiled for 2 hr. with sodium hydroxide (100 g.) in water (100 ml.) and ethanol (1500 ml.). Most of the alcohol was removed by distillation and the residue was diluted with water. The suspension of solid was shaken with chloroform : it dissolved and, almost immediately, a crystalline hydrate separated which was filtered off and boiled with benzene in a flask fitted with a water separator and condenser. As water was removed, the solid went into solution. The solution was decolorized with charcoal, filtered, and allowed to cool : 23a-*bromo*-5α : 25D-*spirostan*-3β : 11β : 12α-*triol* (26·3 g., 55%) [m. p. 187—189° (decomp.)]. Crystallisation from benzene gave material of m. p. 190—192° (decomp.), $[\alpha]_D$ −26° (*c* 0·86). For analysis, a specimen was dried at 120°/0·1 mm. for 4 hr. (Found : C, 61·4; H, 8·6. $C_{27}H_{43}O_5Br$ requires C, 61·5; H, 8·2%) and had $\nu_{max.}$ (in Nujol) 3620 and 3430 (OH), 1016, 951, 914, and 722 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

An experiment in which the time of reaction of epoxide with trichloroacetic acid was extended to 7 days gave a 54% yield of the triol.

3β : 12α-*Diacetoxy*-23a-*bromo*-5α : 25D-*spirostan*-11β-*ol* (XII; R = R′ = Ac, X = Br).—The above triol (5 g.) was shaken at room temperature with pyridine (50 ml.) and acetic anhydride (50 ml.) for 16 hr., during which the solid dissolved. The mixture was distilled to dryness under reduced pressure and the last trace of acetylating mixture removed by refluxing the residual gum for 15 min. with methanol and again evaporating. Crystallisation of the residue from a little methanol gave the *diacetate* (3·04 g.), m. p. 195—198° (decomp.), and a second crop (1·89 g.), m. p. 194—196° (decomp.) (total yield 85%). Purification by chromatography and crystallisation from methanol gave needles, m. p. 201—203° (decomp.), $[\alpha]_D$ −23·4° (*c* 1·6) (Found : C, 60·7; H, 7·85. $C_{31}H_{47}O_7Br$ requires C, 60·9; H, 7·75%), $\nu_{max.}$ (in CS_2) 3620 and 3550 (OH), 1738 and 1236 (OAc), 1024, 944, 914, and 722 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

3β : 12α-*Diacetoxy*-23a-*bromo*-5α : 25D-*spirostan*-11-*one* (XIII; R = Ac, X = Br).—Chromic anhydride (flake; 2·4 g.) was added to pyridine (40 ml.) with stirring and water-cooling. When formation of the complex was complete (*ca.* 1 hr.) a solution of 3β : 12α-diacetoxy-23*a*-bromo-5α : 25*D*-spirostan-11β-ol (3·0 g.) in pyridine (30 ml.) was added and the mixture was stirred for 4 hr. An equal volume of benzene was added and the mixture was filtered. The residue was washed with cold benzene, and the combined filtrate and washings were washed successively with water, 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. The solution was dried ($MgSO_4$) and evaporated. Crystallisation of the residual gum from methanol gave the *ketol diacetate* (2·26 g., 76%), m. p. 164—166°. Further crystallisation from the same solvent raised the m. p. to 168—171°; $[\alpha]_D$ was +7·2° (*c* 1·27) (Found : C, 61·3; H, 7·3. $C_{31}H_{45}O_7Br$ requires C, 61·1; H, 7·4%). Infrared spectrum : see ref. 13.

23a-*Bromo*-3β : 12α-*dihydroxy*-5α : 25D-*spirostan*-11-*one* (XIII; R = H, X = Br).—The foregoing diacetate (0·25 g.) in ethanol (25 ml.) was treated with a solution of potassium hydroxide (1·25 g.) in the minimum volume of water, and the solution was left overnight at room temperature, then poured into water. A solid separated which was filtered off, washed with water, and dried. Crystallisation from acetone gave the *ketol* as needles, m. p. 209—211° (decomp.), $[\alpha]_D$ −7·7° (*c* 0·83) (Found : C, 61·5; H, 7·9. $C_{27}H_{41}O_5Br$ requires C, 61·7; H,

7·9%), $\nu_{max.}$ (in Nujol) 3620 and 3430 (OH), 1695 (CO), 1008, 942, 918, and 720 cm.$^{-1}$ (23*a*-bromo-25*D*-spirostan).

The m. p. of this material depended greatly on the rate of heating and apparently on the solvent used for crystallisation.

The ketol did not reduce Fehling's solution.

Reacetylation of the ketol with pyridine and acetic anhydride, overnight at room temperature, gave the original diacetate (XIII; R = Ac, X = Br).

5α : 25D-*Spirostan*-3β : 11β : 12α-*triol* (XII; R = X = H).—23*a*-Bromo-5α : 25*D*-spirostan-3β : 11β : 12α-triol (20 g.), zinc dust (acid washed; 100 g.), and acetic acid (200 ml.) were boiled together with stirring for 2 hr. The solution was filtered and the residue was washed with boiling acetic acid. The combined filtrate and washings were evaporated to small bulk under reduced pressure and diluted with water. The solid was filtered off, washed with water, and dried. This partially acetylated material was hydrolysed with a boiling mixture of 40% aqueous sodium hydroxide (40 ml.) and ethanol (400 ml.) for 2 hr. Most of the solvent was distilled off and the residue was diluted with water. The precipitated solid crystallised from aqueous methanol (charcoal) in two crops, giving 13·37 g. (79%) of material, m. p. 247—251°. Crystallisation from acetonitrile gave the pure *triol*, m. p. 250—254°, $[\alpha]_D$ −33° (*c* 0·85) (Found: C, 72·4; H, 10·0. $C_{27}H_{44}O_5$ requires C, 72·3; H, 9·9%), $\nu_{max.}$ (in Nujol) 3430 (OH), 979, 920, 898, and 861 cm.$^{-1}$ (25*D*-spirostan).

3β : 12α-*Diacetoxy*-5α : 25D-*spirostan*-11β-*ol* (XII; R = Ac, X = H).—The foregoing triol (11·64 g.) was shaken overnight at room temperature with pyridine (116 ml.) and acetic anhydride (116 ml.). The product was worked up as in the preparation of the 23-bromo-compound. Crystallisation from methanol gave 11·49 g. (83%) of material, m. p. 235—238°. Further crystallisation from aqueous dioxan gave the *diacetate*, m. p. 239—241°, $[\alpha]_D$ −29° (*c* 0·87) (Found: C, 69·95; H, 9·1. $C_{31}H_{48}O_7$ requires C, 69·9; H, 9·1%), $\nu_{max.}$ (in CS_2) 3620 and 3550 (OH), 1732—1722 and 1240—1230 (acetates), 978, 918, 895, and 862 cm.$^{-1}$ (25*D*-spirostan).

3β : 12α-*Diacetoxy*-5α : 25D-*spirostan*-11-*one* (XIII; R = Ac, X = H).—The oxidation was carried out as described above for the 23-bromo-derivative with the foregoing triol diacetate (10 g.) in pyridine (120 ml.) added to the complex prepared from chromic anhydride (9·5 g.) and pyridine (160 ml.). Crystallisation from methanol gave 7·12 g., m. p. 186—190°, and a second crop (1·30 g.), m. p. 181—185° (total yield 84·5%). Further crystallisation from methanol gave the *ketol diacetate* as needles, m. p. 188—190°, $[\alpha]_D$ +5·3° (*c* 0·94) (Found: C, 70·4; H, 8·5. $C_{31}H_{46}O_7$ requires C, 70·15; H, 8·7%), $\nu_{max.}$ (in CS_2) 1756 and 1218 (displaced OAc), 1735 and 1238 (OAc), 1735 (displaced CO), 978, 918, and 895 cm.$^{-1}$ (25*D*-spirostan).

3β : 12α-*Dihydroxy*-5α : 25D-*spirostan*-11-*one* (XIII; R = X = H).—The diacetate (4·5 g.) was hydrolysed with potassium hydroxide (22·5 g.) in aqueous ethanol (450 ml.) as described for the preparation of the 23-bromo-analogue. The *ketol* (3·54 g., 93%) separated from aqueous acetone as crystals, m. p. 257—258°. Further crystallisation from aqueous acetone gave material, m. p. 250—255°, $[\alpha]_D$ −13·2° (*c* 1·17). For analysis it was dried in a high vacuum at 140° (Found: C, 72·5; H, 9·8. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%), $\nu_{max.}$ (in Nujol) 3400 (OH), 1703 (CO), 976, 918, 895, and 865 cm.$^{-1}$ (25*D*-spirostan).

Crystallisation from methanol appeared to give a different form which, even after being heated at 140° *in vacuo*, was solvated. It melted at 251—255° (Found: C, 71·25; H, 9·45. $C_{27}H_{42}O_5,\frac{1}{2}MeOH$ requires C, 71·4; H, 9·6%), and had $\nu_{max.}$ (in Nujol) 3400 (OH), 1694 and 1708 (CO), 980, 920, 892 and 865 cm.$^{-1}$ (25*D*-spirostan). When dissolved in chloroform, the two forms had identical spectra, except as due to the presence of methanol in the solvated form. The splitting of the carbonyl stretching band in the Nujol spectrum of the solvated form is attributed to intermolecular hydrogen bonding.

The ketol did not reduce Fehling's solution. Reacetylation at room temperature overnight with pyridine and acetic anhydride gave the diacetate (XIII; R = Ac, X = H).

Debromination of 3β : 12α-*Diacetoxy*-23a-*bromo*-5α : 25D-*spirostan*-11-*one*.—The ketol diacetate (250 mg.) was boiled for 2 hr. with zinc dust (acid-washed; 1 g.) and acetic acid (2·5 ml.). The crude product (210 mg.), isolated in the usual way, had m. p. 168—174°, $[\alpha]_D$ +3°. The infrared spectrum was virtually identical with that of an authentic specimen of (XIII; R = Ac, X = H). Crystallisation from methanol gave 120 mg. of material with m. p. 180—183°.

Action of Alkali upon 3β : 12α-*Dihydroxy*-5α : 25D-*spirostan*-11-*one and its Diacetate*.—(a) *Sodium hydroxide in aqueous* tert.-*butyl alcohol*. Treatment of the diacetate with a boiling mixture of 1·25N-aqueous sodium hydroxide and an equal volume of *tert.*-butyl alcohol for 6 hr. merely caused hydrolysis of the ester groupings. The crude product had m. p. 240—250° and $[\alpha]_D$ −12·5°; reacetylation gave the original diacetate, m. p. 178—194°, $[\alpha]_D$ +4°.

(b) *Potassium hydroxide in aqueous dioxan.* Treatment of the diacetate with equal volumes of 0·9N-aqueous potassium hydroxide and dioxan at the b. p. for 6 hr. gave a crude dihydroxy-ketone with $[\alpha]_D$ −26°, corresponding to a 50% conversion into the 12β-epimer (it being assumed that no other change occurred simultaneously); after 24 hours' treatment the crude product had $[\alpha]_D$ −33° and acetylation gave a crude diacetate, m. p. 204—211°, $[\alpha]_D$ −64° (corresponding to 82% epimerisation). Crystallisation of this material gave 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one (VIII; R = Ac) (about 50%), m. p. 221—225°, $[\alpha]_D$ −77°, infrared spectrum identical with that of authentic material.

(c) *With alcoholic sodium hydroxide.* Treatment of the diacetate with 4N-sodium hydroxide in boiling 85% ethanol for 2 hr. and reacetylation gave material with $[\alpha]_D$ −64° (82% epimerisation); material obtained similarly after 6 hours' refluxing had $[\alpha]_D$ −69° (88% epimerisation). The crude dihydroxy-ketone obtained by 6 hours' hydrolysis of the diacetate (250 mg.) was treated in the usual way with Girard reagent P. From the " ketonic fraction " only 10 mg. of a gum were isolated; the non-reactive fraction was acetylated in the usual way and the product was crystallised from ethanol, to give 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one (VIII; R = Ac) (184 mg., 74%), m. p. 223—226°, $[\alpha]_D$ −78·5°. Hydrolysis of the crystallisation residues and paper chromatography [cf. 24] showed the presence of the ketone (VIII; R = H), of a substance with an R_F value close to that of the α-hydroxy-epimer (XIII; R = X = H), and of a much more polar compound, probably a triol.

5α : 25D-*Spirostan*-3β : 11α : 12α-*triol* (XIV; R = H).—A solution of 3β-acetoxy-5α : 25*D*-spirost-11-en [42] (2·0 g.) in ether (125 ml.) containing pyridine (1 ml.) was treated with osmium tetroxide (1·0 g.) in ether (25 ml.). The mixture was left overnight and the osmium complex was filtered off, washed with ether, and boiled under reflux for 4½ hr. with sodium sulphite (18 g.) in ethanol (160 ml.) and water (80 ml.). The cooled mixture was filtered and the solid washed with boiling ethanol. The combined filtrate and washings were evaporated to small bulk under reduced pressure. Dilution of the residue with water gave the crude triol (1·48 g., 75%), m. p. 220—230°. After recrystallisation from aqueous ethanol or ethyl acetate–light petroleum, the substance had m. p. 226—228°, $[\alpha]_D$ −61° (*c* 1·7), $\nu_{max.}$ (in Nujol) 3400 (OH), 980, 918, 898, and 862 cm.$^{-1}$ (25*D*-spirostan). Hirschmann *et al.*[33] give m. p. 221—225°.

Acetylation of the triol with equal volumes of acetic anhydride and pyridine at 100° for 75 min. gave the *triacetate*, which was difficult to purify. Addition of water to a cold ethanolic solution gave it as a solid, m. p. 115—125°, $[\alpha]_D$ −49° (*c* 1) (Found: C, 69·1; H, 8·7. $C_{33}H_{50}O_8$ requires C, 69·0; H, 8·8%), $\nu_{max.}$ (in CS_2) 1738 and 1240 (OAc), 980, 920, 898, and 862 cm.$^{-1}$ (25*D*-spirostan).

Acknowledgment is made to Mr. W. F. Wall for assistance in the experimental work.

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[42] Elks, Phillipps, Taylor, and Wyman, *J.*, 1954, 1739.

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836. *Studies in the Synthesis of Cortisone. Part XVI.* A New Method of Preparing* 11-*Oxotigogenin.*†

By J. H. CHAPMAN, J. ELKS, G. H. PHILLIPPS, and L. J. WYMAN.

Attempts to prepare 11-oxotigogenin by the action of zinc upon 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one ‡ or its carboxylic or sulphonic esters failed. However, the esters were readily reduced to the required ketone by alkali or alkaline-earth metals in liquid ammonia, particularly good results attending the use of calcium. Under the same conditions, reduction of the unesterified ketol yields 5α : 25*D*-spirostan-3β : 11α : 12β-triol.

The behaviour of 3β : 12α-dihydroxy-5α : 25*D*-spirostan-11-one and its diacetate towards these reducing agents parallels, for the most part, that of the 12β-epimers.

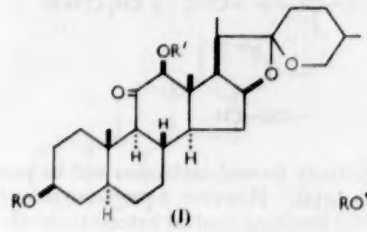
THE method that has been used in the bile-acid series to convert a 12β-hydroxy-11-ketone into the 11-ketone itself, namely, replacement of the hydroxyl group by bromine and

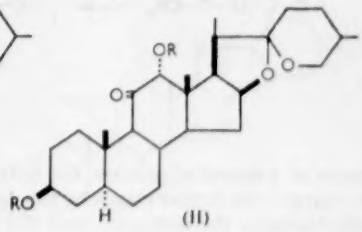
* Part XV, preceding paper.

† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

‡ See footnote † on p. 4330.

subsequent debromination,[1,2] is inapplicable to the spirostan series because of the instability of the spiroketal side-chain to acid reagents (see preceding paper). Mueller *et al.*[3] attempted, without success, to reduce 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (I; R = R′ = H)


(I)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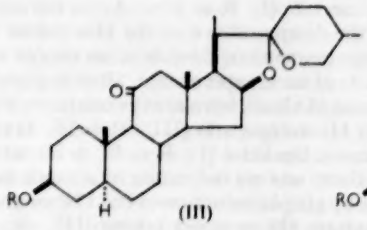
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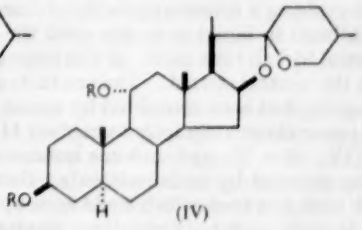

(IV)

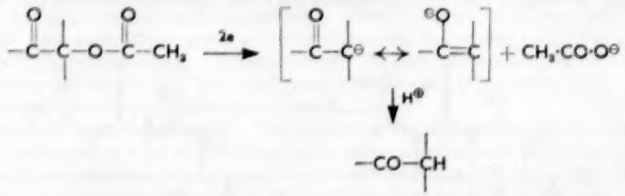
with sodium amalgam; moreover, both the free ketol and its diacetate were resistant to the action of zinc. Rosenfeld and Gallagher[4] recently reported that in the 11 : 12-ketols of the cholanic acid series the axial 11β- and 12α-acetoxy-groups can be removed by prolonged treatment with zinc and acetic acid; the equatorial 11α- and 12β-acetoxy-groups were much more resistant, though not wholly inert. In a number of experiments with 3β : 12β- (I; R = R′ = Ac) and 3β : 12α-diacetoxy-5α : 25*D*-spirostan-11-one (II; R = Ac) and the corresponding free alcohols (I; R = R′ = H) and (II; R = H), we obtained no evidence that zinc was causing removal of the substituent from $C_{(12)}$ to a significant degree. With very drastic conditions (100 parts of zinc in boiling acetic acid for 24 hours), the diacetates underwent some reaction, probably the desired one, as indicated by the infrared spectra of the crude products, but even then 50% or more of the ketol derivative remained.

The readiness of sulphonic esters to undergo fission of the C–O bond has suggested their use in this problem. However, in both the cholanic acid[1] and the spirostan series[3,5] a 12β-methanesulphonyloxy- or 12β-toluene-*p*-sulphonyloxy-group proved extraordinarily resistant both to replacement by iodine and to reductive removal. We attempted to reduce 3β-acetoxy-12β-methanesulphonyloxy-5α : 25*D*-spirostan-11-one (I; R = Ac, R′ = $Me{\cdot}SO_2$) with zinc, zinc–copper, or zinc–copper–nickel, with chromous chloride, and with hydriodic acid, but the ketol derivative was unaffected by any of them. In agreement with the work of Djerassi *et al.*[5] on the corresponding toluene-*p*-sulphonate, the methanesulphonate was reduced by lithium aluminium hydride to 5α : 25*D*-spirostan-3β : 11β : 12β-triol, the S–O bond rather than the $C_{(12)}$–O bond having been split. A slow reaction occurred between the methanesulphonate and lithium chloride in boiling dimethylformamide, but the yield of crystalline product was too low to permit identification.

3β : 12β-Diacetoxy-5α : 25*D*-spirostan-11-one (I; R = R′ = Ac) was finally converted into 11-oxotigogenin (III; R = H) by means of metal and liquid ammonia systems. This

[1] Borgstrom and Gallagher, *J. Biol. Chem.*, 1949, **177**, 951.
[2] Hershberg, Herzog, Coan, Weber, and Jevnik, *J. Amer. Chem. Soc.*, 1952, **74**, 2585.
[3] Mueller, Norton, Stobaugh, Lin Tsai, and Winniford, *ibid.*, 1953, **75**, 4892.
[4] Rosenfeld and Gallagher, *ibid.*, 1955, **77**, 4367.
[5] Djerassi, Ringold, and Rosenkranz, *ibid.*, 1954, **76**, 5533.

reduction of an α-acetoxy-ketone may, by analogy with the fission of allyl and benzyl alcohols and their derivatives, be represented as follows : [6]



In the absence of a source of protons, the initially formed carbanion will be protected by its negative charge from further attack by the metal. However, a proton source of sufficient strength will discharge the carbanion, and the resulting neutral ketone molecule will then be liable to further reduction by excess of metal.[7] We attempted to avoid such over-reduction by adding a solution of the ketol diacetate (I; R = R′ = Ac) in tetrahydrofuran to one of lithium in liquid ammonia until the disappearance of the blue colour indicated that the metal had all been used; at this stage ammonium chloride or an alcohol was added to liberate the neutral steroid. The products of such experiments, after hydrolysis of the 3-acetoxy-group had been completed by means of alkali, were always mixtures, which were shown by paper chromatography to contain 11-oxotigogenin (III; R = H), 11α-hydroxytigogenin (IV; R = H), and, in some instances, the ketol (I; R = R′ = H) derived from the starting material by hydrolysis only; there was no indication of a much more polar compound, such as a triol, which could arise by simple reduction of the 11-oxo-group of the ketol (I; R = R′ = Ac). From these mixtures the required ketone (III; R = H) was isolated in only about 20% yield.

Attention was then turned to metals other than lithium. Neither sodium nor potassium was satisfactory, for the products obtained by the titration technique contained much ketol (I; R = R′ = H). Calcium, on the other hand, gave a product that appeared, from paper-chromatographic studies, to contain neither the ketol (I; R = R′ = H) nor the diol (IV; R = H), and, from it, nearly pure 11-oxotigogenin was isolated in *ca.* 70% yield. Barium was found to be as good as calcium, but had no advantage.

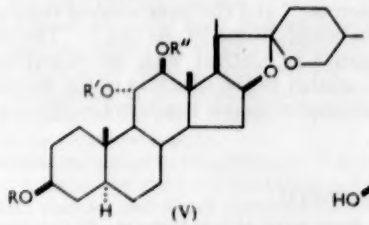
The titration technique was not particularly convenient, and variations in the purity of the calcium, as well as uncertainties about the stoicheiometry of the reaction (see below), ruled out the possibility of using the exact amount of metal required. A more suitable method was found in the use of an excess of calcium and later removal of the final excess by addition of bromobenzene; this compound, unlike the more conventional reagents, caused no over-reduction. An additional practical improvement was the replacement of tetrahydrofuran by toluene which was more readily purified and which, in spite of its immiscibility with liquid ammonia, was satisfactory as long as stirring was effective. By these means, the yield of 11-oxotigogenin (isolated as its benzoate) from the ketol diacetate (I; R = R′ = Ac) was raised to 80—84%.

Calcium–ammonia reduction of the free ketol (I; R = R′ = H) gave a completely different result; the major product had the composition of a spirostan-triol [a minor product was 11α-hydroxytigogenin (IV; R = H)]. By analogy with the reduction of 11-oxo-steroids to 11α-hydroxy-steroids by lithium in liquid ammonia in presence of a source of protons [7] (the unprotected hydroxyl groups could act as such a source in this instance), this compound was assigned the structure, 5α : 25*D*-spirostan-3β : 11α : 12β-triol (V; R = R′ = R″ = H), which was confirmed when Wendler *et al.*[8] described the production of the triol (V; R = R′ = R″ = H) along with the diol (IV; R = H) from the ketol (I; R = R′ = H) by reduction with sodium and butan-1-ol.

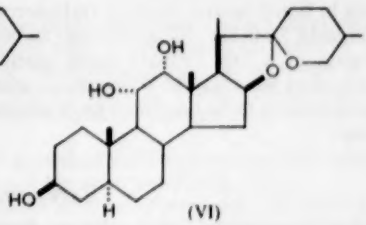
The difference in behaviour between the free ketol (I; R = R′ = H) and its diacetate might be ascribed to initial salt formation by the 12β-hydroxy-group in the former, with

[6] Birch, *Quart. Rev.*, 1950, **4**, 69.
[7] Cf. Sondheimer, Mancera, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1953, **75**, 1282.
[8] Wendler, Hirschmann, Slates, and Walker, *ibid.*, 1955, **77**, 1632.

consequent protection of the $C_{(12)}$–O bond from fission by further electron attack. This, is made less probable, however, by the fact that the course of reduction of the ketol was the same in the presence or the absence of methanol (cf. ref. 6). The possibility that the presence of a proton source, as such, was responsible for preferential attack on the carbonyl



(V)



(VI)

group in the free ketol was ruled out by an experiment in which the ketol diacetate (I; R = R′ = Ac) was reduced with calcium in ammonia in presence of methanol; the product was almost entirely 11α-hydroxytigogenin (IV; R = H), the triol (V; R = R′ = R″ = H) being present only in minute amounts.

Since a likely reason for the different behaviour of the free ketol and its diacetate lies in the electron-withdrawal effect provided by the carbonyl of the 12β-acetoxy-group in the latter, the effect of varying the 12-acyloxy-group was investigated. A more powerful electron-withdrawal effect was provided in 3β-acetoxy-12β-methanesulphonyloxy-5α : 25*D*-spirostan-11-one (I; R = Ac, R′ = Me·SO_2), but reduction of this ester under the usual conditions gave 11-oxotigogenin in yield somewhat inferior to that obtained from the diacetate; the same was true of the dibenzoate (I; R = R′ = Bz). With the di*iso*butyrate (I; R = R′ = Pr^i·CO) steric hindrance apparently reduced the reactivity of the $C_{(12)}$–O bond, the product being a mixture of 11-oxotigogenin (III; R = H) and the ketol (I; R = R′ = H); there was, however, no indication from paper chromatography that the triol was being formed in significant amount. As would be expected from the experiments described above, the 3-monoesters (I; R = Ac or Bu^t·CO, R′ = H) gave none of the 11-oxo-compound, the products of reduction being mixtures of the triol (V; R = R′ = R″ = H) with the original ketol (I; R = R′ = H).

Reduction of 3β : 12α-diacetoxy-5α : 25*D*-spirostan-11-one (II; R = Ac) with calcium and liquid ammonia again gave 11-oxotigogenin (III; R = H) in high yield. The corresponding ketol (II; R = H) might, by analogy with its 12β-epimer, have been expected to yield predominantly 5α : 25*D*-spirostan-3β : 11α : 12α-triol (VI), but it gave a mixture that appeared, from paper chromatography and rotation measurements, to consist of roughly equal amounts of the triol (VI) and 11α-hydroxytigogenin (IV; R = H). The greater ease of cleavage of the axial $C_{(12\alpha)}$–O bond, compared with that of the equatorial $C_{(12\beta)}$–O bond invites comparison with Rosenfeld and Gallagher's work on the relative ease of reduction of axial and equatorial α-acetoxy-ketones by zinc [4] (see above).

The stoicheiometry of the reduction is somewhat obscure. In rough titration experiments, the ketol diacetate (I; R = R′ = Ac) was found to react with 2·8—3·2 g.-atoms of calcium or 6—8 g.-atoms of lithium. On the basis of the reaction scheme suggested above, cleavage of the 12β-acetoxy-group would require only 1 g.-atom of the former, or 2 g.-atoms of the latter metal. However, reaction is certainly not confined to that centre, for the crude product, before alkaline hydrolysis, exists largely as the free 3-hydroxy-compound. It has been shown by Kharasch *et al.*[9] that the ethyl esters of various carboxylic acids will react with 2 g.-atoms of sodium in liquid ammonia to give rather complex mixtures, containing the acyloin and, in some instances, the aldehyde corresponding to the acid fragment of the ester. We have obtained evidence for the formation of acetaldehyde in our experiments, for the toluene recovered from reductions in this solvent was found to be contaminated by crotonaldehyde. Nevertheless, both of these reactions would account for the

[9] Kharasch, Sternfeld, and Mayo, *J. Org. Chem.*, 1940, **5**, 362.

consumption of only 2 g.-atoms of calcium per mole of steroid, and it must be assumed that further reduction occurs of one or both of the two carbon residues split from the molecule.

There have been two references in the recent literature to reactions similar to those described in this paper. Treatment of 6β-hydroxytestosterone (the vinylogue of an α-ketol) with lithium in liquid ammonia gives testosterone,[10] and the same reagent reduces 3β : 5α-dihydroxyergosta-7 : 9(11) : 22-trien-6-one to ergost-22-ene-3β : 6α-diol.[11] The removal, in both instances, of a free hydroxy-group stands in contrast with our experience; it is, however, not clear whether the difference is related to the situation of the hydroxy-group in the steroid nucleus or to the presence or absence of double bonds in conjugation with the ketone group.

Experimental

For general experimental information see Part XIII of this series.[12] Chromatography on paper was carried out as described elsewhere.[13]

Metal–ammonia reductions were carried out in uninsulated 3-necked flasks, fitted with a dropping funnel, a glass stirrer passing through a fibre-washer, and a short air-condenser, plugged at the top with cotton-wool. Liquid ammonia was run rapidly from a cylinder into the flask, and sufficient of the metal was added to impart a permanent blue colour to the liquid. The stated weight of metal was then added during about 5 min. and the solution was stirred gently for 10 min. (except for lithium, for which the time was reduced to 1 min.) before the solution of steroid was added.

Action of Lithium Aluminium Hydride on 3β-Acetoxy-12β-methanesulphonyloxy-5α : 25D-spirostan-11-one.—The methanesulphonate[14] (2·0 g.) in tetrahydrofuran (80 ml.) was added to a suspension of lithium aluminium hydride (2·0 g.) in tetrahydrofuran (20 ml.). The suspension was boiled under reflux for 2 hr. and the excess of hydride was decomposed by addition of ethyl acetate. After acidification the product was extracted with ether, precipitated from methanol by means of water, and chromatographed on alumina. Benzene, ether, and mixtures thereof eluted gums that could not be purified, but 1 : 4 methanol–ether gave a solid which, on crystallisation from aqueous methanol, yielded 5α : 25*D*-spirostan-3β : 11β : 12β-triol (0·17 g.), m. p. 253—256°, $[\alpha]_D$ −67°. This material was identified by its m. p. and infrared spectrum with an authentic sample prepared as described by Djerassi *et al.*,[15] who give m. p. 262—263° and $[\alpha]_D$ −64°.

Reduction of 3β : 12β-Diacetoxy-5α : 25D-spirostan-11-one.—(a) *With calcium and liquid ammonia in absence of an alcohol.* A solution of the ketol diacetate (15 g.) in toluene (200 ml.) was dried by concentration to 150 ml. at normal pressure. The solution was cooled to room temperature and was then added with vigorous stirring to a solution of calcium turnings (4·2 g.) in liquid ammonia (500 ml.). The addition was made in 5 min., the mixture was stirred for a further 3 min., and excess of calcium was then destroyed by the dropwise addition of bromobenzene (*ca.* 4 ml.). Water (5 ml.) was added cautiously and the ammonia was allowed to evaporate. The toluene was removed by distillation on the steam-bath under reduced pressure and methanol (200 ml.) was added to the residue, followed by a solution of potassium hydroxide (5 g.) in water (10 ml.). The mixture was boiled for 1 hr., water (50 ml.) was added, and the mixture was warmed for 30 min. on the steam-bath in order to coagulate the product. Water (250 ml.) and acetic acid (15 ml.) were added, the mixture was cooled, and the product was filtered off, washed thoroughly with water, and dried. The crude 11-oxotigogenin so obtained weighed 12·3 g. and had m. p. 209—218° and $[\alpha]_D$ −31°.

This material in pyridine (120 ml.) was benzoylated by addition of benzoyl chloride (12 ml.). After 2 hr., water (20 ml.) was added to destroy excess of reagent, and the product was precipitated after a further 2 hr. by addition of more water (200 ml.). Addition of boiling methanol (135 ml.) to a solution of the substance in boiling chloroform (45 ml.) gave *11-oxotigogenin benzoate* as lances (11·5 g.), m. p. 228—232°, $[\alpha]_D$ −32° (*c*, 2). A further 1·05 g. were obtained

[10] Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226.
[11] Zürcher, Heusser, Jeger, and Geistlich, *Helv. Chim. Acta*, 1954, **37**, 1562.
[12] Elks and Phillipps, *J.*, 1956, 4320.
[13] Brooks, Hunt, Long, and Mooney, *J.*, in the press.
[14] Elks, Phillipps, Walker, and Wyman, preceding paper.
[15] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278.

from the mother-liquors by evaporation and repeated crystallisation. The total yield was 12·55 g., 83%.

A sample of 11-oxotigogenin benzoate, prepared in a similar way from authentic 11-oxotigogenin, melted at 231—233° and had $[\alpha]_D$ −32° (*c* 1·0) (Found: C, 76·5; H, 8·6. $C_{34}H_{44}O_5$ requires C, 76·4; H, 8·7%), $\nu_{max.}$ (in CS_2) 3100, 1715, 1272, 1171, 706 (OBz), 1715 (CO), 981, 920, and 895 cm.$^{-1}$ (25*D*-spirostan).

If the toluene recovered from such an experiment was shaken with a saturated solution of 2 : 4-dinitrophenylhydrazine in 2*N*-hydrochloric acid, a precipitate appeared in the aqueous layer and, on further shaking, redissolved in the toluene layer. Evaporation of the toluene and chromatography of the residue gave crotonaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 189° after crystallisation from ethanol. It was identified by mixed m. p. and infrared spectroscopy with an authentic sample.

In a similar reduction to the above, on 50 g. of the ketol diacetate, and with tetrahydrofuran in place of toluene, the yield of 11-oxotigogenin benzoate was 83·5%.

(b) *With calcium and liquid ammonia in the presence of methanol.* A solution of calcium (7·0 g.) in liquid ammonia (1400 ml.) was stirred while a 2·08% solution of 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one in 4 : 1 dioxan–methanol was added slowly. The blue colour of the liquid ammonia solution was discharged when 70 ml. of the solution (equiv. to 1·46 g. of ketol diacetate) had been added. The addition was stopped at this point and methanol (20 ml.) was added carefully. The ammonia was removed and water was added, followed by sufficient concentrated hydrochloric acid to bring the pH to about 2. The solid (1·16 g.) was filtered off and washed with water and was then boiled for 2 hr. with a mixture of 40% aqueous sodium hydroxide (8 ml.) and ethanol (90 ml.). Most of the solvent was distilled off and the residue was diluted with water, to precipitate a solid (1·13 g.), m. p. 214—218°, $[\alpha]_D$ −76°.

Paper chromatography of this material showed one main spot with the R_F of 11α-hydroxytigogenin; very faint spots corresponded to 5α : 25*D*-spirostan-3β : 11α : 12β-triol and to 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one.

Crystallisation of the solid (1·04 g.) from acetonitrile gave 0·70 g. (64%) of 11α-hydroxytigogenin, m. p. 212—217°. The infrared spectrum was identical with that of an authentic sample.

Acetylation of the diol (250 mg.) with acetic anhydride and pyridine on the steam-bath for 90 min. gave the diacetate as needles (0·21 g.), m. p. 172—174°, $[\alpha]_D$ −83°, after crystallisation from methanol. The material was identified by mixed m. p. and infrared spectrum with an authentic specimen.

Sondheimer *et al.*[7] give m. p. 218—220°, $[\alpha]_D$ −78°, for 11α-hydroxytigogenin and m. p. 174—176°, $[\alpha]_D$ −79°, for the diacetate.

Reduction of 3β : 12β-*Dihydroxy-5α* : 25D-*spirostan*-11-*one with Calcium and Liquid Ammonia.*—A solution of the ketol (20 g.) in tetrahydrofuran (sodium-dried; 200 ml.) was added, during about 20 min., to a solution of calcium (4 g.) in liquid ammonia (400 ml.). The mixture was stirred for a further 30 min. and an excess of ethanol was added carefully. The ammonia was allowed to evaporate, and water was added, followed by sufficient concentrated hydrochloric acid to bring the pH to about 2. The mixture was stirred vigorously during these additions and until a granular solid separated. After being left for some hours in the refrigerator, the solid (19 g.) was filtered off. Crystallisation from ethyl acetate gave 12·7 g. of 5α : 25*D*-spirostan-3β : 11α : 12β-triol, m. p. 248—250°, $[\alpha]_D$ −65°, and a further crop (1·45 g.) of slightly lower m. p. This material was impure; the presence of unchanged ketol and of 11α-hydroxytigogenin was indicated by infrared spectroscopy and by chromatography of the acetylated material (see below). Wendler *et al.*[8] give m. p. 256—258°, $[\alpha]_D$ −65·4°.

The crude triol was acetylated with pyridine (80 ml.) and acetic anhydride (80 ml.) overnight at room temperature. The product (16·0 g.) was chromatographed on alumina (Peter Spence, Grade O: 450 g.), to give the following, in order of decreasing ease of elution:

3β : 11α-Diacetoxy-5α : 25*D*-spirostan (0·42 g.), m. p. 173—175°, after recrystallisation from methanol.

3β : 12β-Diacetoxy-5α : 25*D*-spirostan-11-one (1·05 g.), m. p. 227—229° after crystallisation from ethanol.

3β : 11α-Diacetoxy-5α : 25*D*-spirostan-12β-ol (0·15 g.), m. p. 204—209°, $[\alpha]_D$ −61·5° (from methanol), $\nu_{max.}$ (in CS_2) 3550 (OH), 1735 and 1238 (OAc), 978, 918, and 896 cm.$^{-1}$ (25*D*-spirostan). Wendler *et al.*[8] give m. p. 206—208°, $[\alpha]_D$ −64·4°.

3β : 12β-Diacetoxy-5α : 25*D*-spirostan-11α-ol (3·8 g.), m. p. 232—233·5°, $[\alpha]_D$ −61·5° (from methanol), $\nu_{max.}$ (in CS_2) 3620 (OH), 1732 and 1240 (OAc), 980, 920, and 898 cm.$^{-1}$ (25*D*-spirostan). Wendler *et al.*[8] give m. p. 231—232°, $[\alpha]_D$ −55·5°.

Acetylation of the triol (1 g.) with boiling acetic anhydride (15 ml.) containing fused sodium acetate (1 g.) for 2½ hr. gave, after chromatography on alumina and crystallisation from methanol, 3β : 11α : 12β-triacetoxy-5α : 25*D*-spirostan (0·31 g.), m. p. 198—200°, $[\alpha]_D$ −58°, $\nu_{max.}$ (in CS_2) 1738 and 1238 (OAc), 978, 918, and 898 cm.$^{-1}$ (25*D*-spirostan). Wendler *et al.*[8] give m. p. 197—198°, $[\alpha]_D$ −53·3°.

When the reduction of 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one was carried out in presence of methanol by the method used for the corresponding diacetate, the major product was, again, 5α : 25*D*-spirostan-3β : 11α : 12β-triol, m. p. 248—250°. Paper chromatography of the crude material showed it to be free from the starting ketol (this was confirmed by the infrared spectrum) but revealed a trace of 11α-hydroxytigogenin. On crystallisation from ethyl acetate the triol separated in polymorphic forms—needles and rosettes—which could be partially separated by hand. The needles melted at 250—253°; the rosettes changed to needles at *ca.* 230° and then melted at 249—250°. The infrared spectra of Nujol mulls showed differences of detail which, however, disappeared in the spectra of bromoform solutions.

Reduction of Other Esters of 3β : 12β-*Dihydroxy*-5α : 25D-*spirostan*-11-*one*.—(a) *Dibenzoate*. A solution of the ketol dibenzoate [14] in pure, dry tetrahydrofuran (3·27% w/v) was added dropwise to a stirred solution of calcium (120 mg.) in liquid ammonia (50 ml.). The colour of this solution was discharged after 15·9 ml. of the solution (equiv. to 0·52 g. of the steroid) had been added. Ammonium chloride (1 g.) and ethanol were added, the ammonia was evaporated off and water was added, followed by excess of hydrochloric acid. The solid was filtered off and boiled with 5% methanolic potassium hydroxide for 1 hr. The product was isolated by means of chloroform and, after crystallisation from ethyl methyl ketone, gave 11-oxotigogenin (0·21 g., 62%), m. p. 219—223°, $[\alpha]_D$ −30°. A second crop (26 mg.) melted at 210—216°. Sondheimer *et al.*[7] give m. p. 223—225°, $[\alpha]_D$ −29°.

(b) 3-*Acetate* 12-*methanesulphonate*. Addition of this ester [14] (1·13 g.) in tetrahydrofuran (10 ml.) to calcium (300 mg.) in liquid ammonia (100 ml.), and subsequent decomposition of excess of calcium with bromobenzene, hydrolysis of the product with methanolic potassium hydroxide, and benzoylation as already described, gave 11-oxotigogenin benzoate (0·703 g., 66%) as rods, m. p. 228—232°, $[\alpha]_D$ −32°.

(c) *Diisobutyrate*. Reduction of the di*iso*butyrate [14] by the titration method as described in (a) gave a crude product, m. p. 195—210°, $[\alpha]_D$ −36°. It was shown by its infrared spectrum and by paper chromatography to be a mixture of 11-oxotigogenin with 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one. The acetate obtained from this mixture melted between 160° and 180° and had $[\alpha]_D$ −52°.

(d) 3-*Monoacetate*. Reduction of the ketol monoacetate [14] in tetrahydrofuran with excess of calcium in liquid ammonia as descibed in (b) gave a crude product having m. p. 223—234°, $[\alpha]_D$ −58°. Paper chromatography suggested the presence of 5α : 25*D*-spirostan-3β : 11α : 12β-triol and 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one.

(e) 3-*Monopivalate*. Reduction of this ester,[14] by the titration technique as in (a) above, gave a product having m. p. 207—223°, $[\alpha]_D$ −52°; paper chromatography suggested that it was a mixture of 5α : 25*D*-spirostan-3β : 11α : 12β-triol and 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one.

Reduction of 3β : 12α-*Diacetoxy*-5α : 25D-*spirostan*-11-*one*.—A solution of the ketol diacetate [14] (0·5 g.) in tetrahydrofuran (10 ml.) was reduced in the usual way with calcium (0·14 g.) in liquid ammonia (50 ml.). Excess of calcium was destroyed with bromobenzene, and the crude product was hydrolysed with methanolic potassium hydroxide. The 11-oxotigogenin (355 mg.), so obtained, melted at 206—213° and had $[\alpha]_D$ −31°. Benzoylation and subsequent crystallisation from chloroform–methanol gave 11-oxotigogenin benzoate (363 mg., 72%), m. p. 228—232°, $[\alpha]_D$ −32°.

Reduction of 3β : 12α-*Dihydroxy*-5α : 25D-*spirostan*-11-*one*.—Reduction of the ketol [14] (250 mg.) in tetrahydrofuran (5 ml.) with excess of calcium in liquid ammonia and removal of excess with bromobenzene gave, after crystallisation of the resulting gum from chloroform–methanol, an impure product (154 mg.), m. p. 211—229°, $[\alpha]_D$ −69°. Paper chromatography suggested the presence of 5α : 25*D*-spirostan-3β : 11α : 12α-triol [14] and 5α : 25*D*-spirostan-3β : 11α-diol; the rotation is consistent with the presence of these compounds in equal proportions.

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837. *Studies in the Synthesis of Cortisone. Part XVII.* The Bromination of Cholestan-3-one.*

By C. W. P. Crowne, R. M. Evans, G. F. H. Green, and A. G. Long.

Base-catalysed bromination of 2α-bromocholestan-3-one gives the corresponding 2 : 2-dibromo-ketone; further halogenation in such conditions yields the unstable 2 : 2 : 4β-tribromocholestan-3-one.

The rearrangement of 2 : 2-dibromocholestan-3-one into its 2α : 4α-dibromo-isomer involves hydrogen bromide as a specific promoter, by means of which molecular bromine is generated from the *gem.*-dibromo-ketone. The ensuing dehalogenation and rehalogenation eventually produce the more stable 2 : 4-dibromo-ketone. Correspondingly, in the acid-catalysed bromination of 2α-bromocholestan-3-one the first-formed 2 : 2-dibromo-compound passes into the 2 : 4-dibromo-isomer as the reversible processes oust the kinetic control.

The dehydrogenation of 3-oxo-5α-steroids to Δ^4-3-keto-steroids calls for the introduction of bromine atoms at $C_{(2)}$ and $C_{(4)}$ before a practicable dehydrobromination can be achieved.[1] In polyoxo-steroids halogenation outside ring A may complicate these stages; consequently we have tried to anticipate such difficulties in the proposed synthesis of cortisone from 5α-steroids by studying the control that may be exerted over the bromination of cholestan-3-one.

Kröhnke and Timmler [2,3] distinguished two stages in the acid-catalysed brominations of simple ketones: the first, a kinetically controlled stage, yielded a compound that might suffer change as the ensuing reversible reactions ($R{\cdot}CO{\cdot}CHBrR' + HBr \longrightarrow R{\cdot}CO{\cdot}CH_2R' + Br_2$) of the second stage reached an equilibrium in which the stable α-bromo-ketones predominated. Corey [4,5] studied similar aspects of the chemistry of α-bromoketo-steroids, and Djerassi and Scholz [6] reported attempts at avoiding these complications in the bromination of steroid ketones: to this end, for instance, they used *N*-bromosuccinimide to make 2 : 2-dibromocholestan-3-one from the 2α-bromo-ketone, so precluding the formation of hydrogen bromide, in whose presence the *gem.*-dibromo-ketone changes into 2α : 4α-dibromocholestan-3-one.[7] Acid-catalysed bromination of 3-oxo-5β-steroids yields mainly the 4-bromo-derivatives, whereas the isomeric 5α-steroids give first the 2-bromo-ketones.[8] The possibility that base-catalysed halogenation of 3-oxo-5α-steroids might be differently ordered therefore attracted us, since it could offer a means of obtaining 4-bromo-3-oxo-5α-steroids.

Our attempts at brominating cholestan-3-one in conditions favouring basic catalysis failed to yield an identifiable product. The presence of an electronegative substituent on the carbon atom next to the carbonyl group should facilitate the release of the proton and hence favour further substitution;[9] confirmation of this reasoning is provided by the bromination of acetone, which under acid catalysis generates α-bromoacetone and then slowly αα′-dibromoacetone (among other products),[10] whereas in basic conditions a haloform reaction takes place.[11] And indeed we found that 2α-bromocholestan-3-one is converted

* Part XVI, preceding paper.

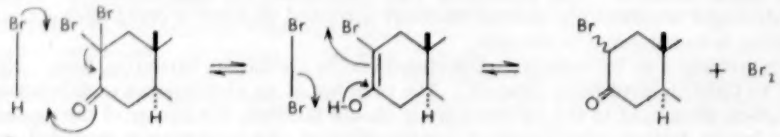
[1] Cf. following paper.
[2] Kröhnke and Timmler, *Ber.*, 1936, **69**, 614.
[3] Kröhnke, *ibid.*, p. 921.
[4] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.
[5] Cf. Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 261.
[6] Djerassi and Scholz, *Experientia*, 1947, **3**, 107.
[7] Inhoffen and Zühlsdorff, *Ber.*, 1943, **76**, 233.
[8] Cf. Taylor, *Chem. and Ind.*, 1954, 250.
[9] Cf. Alexander, "Ionic Organic Reactions," Wiley and Sons, Inc., New York, 1950, p. 206.
[10] Hughes, Watson, and Yates, *J.*, 1931, 3318; Watson, Nathan, and Laurie, *J. Chem. Phys.*, 1935, **3**, 170; Weygand and Schmied-Kowarzik, *Chem. Ber.*, 1949, **82**, 335; Kröhnke and Lüderitz, *ibid.*, 1950, **83**, 60.
[11] Cf. Fuson and Bull, *Chem. Rev.*, 1934, **15**, 275; Bell *et al.*, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88; 1949, *A*, **198**, 308.

efficiently, in acetic acid containing potassium or sodium acetate as the base, into 2 : 2-dibromocholestan-3-one, with no polarimetric or spectroscopic evidence of the formation of an isomeric 2 : 4-dibromo-compound. When sodium acetate is used only as a buffer with an acid catalyst the bromination stops at monosubstitution;[12] further substitution in these conditions is thwarted because the bromo-ketone is less easily enolised than its precursor, and it becomes possible only if the buffer is omitted or if so much of the acetate is added that a base-catalysed halogenation of the bromo-ketone occurs.

The influence of the halogen substituents on the halogenation of α-halogeno-ketones is transmitted across the carbonyl group: thus the base-catalysed bromination of ααα-trifluoroacetone is facilitated by the accumulation of halogen atoms on the seemingly remote carbon atom, and the acid-catalysed halogenation is retarded.[13] Accordingly 2 : 2-dibromocholestan-3-one affords by base-catalysed bromination an unstable tribromo-derivative, $[\alpha]_D$ +60°, which we consider to be 2 : 2 : 4β-tribromocholestan-3-one on account of its strong carbonyl absorption[14] at 1735 cm.$^{-1}$. Ellis and Petrow[15] noticed the slow acid-catalysed bromination of 2 : 2-dichlorocholestan-3-one to give a dichlorobromo-ketone, $[\alpha]_D$ +61·5°, and the similarity of the molecular rotations suggests that their product is 4β-bromo-2 : 2-dichlorocholestan-3-one; however, the survival in a solution containing hydrogen bromide of a compound with an axial C–Br bond presents an anomaly to which we shall refer later.

The acid-catalysed monobromination of a 3-oxo-5α-steroid, with subsequent base-catalysed halogenation, bids fair to yield 2 : 2-dibromo-3-oxo-5α-steroids selectively, even when there are other keto-groups in the molecule. If the rearrangement of such compounds could be kept to ring A, *i.e.*, if it is of the intramolecular type, a nice control could be exerted over the formation of the 2 : 4-dibromo-3-oxo-system in polyoxo-steroids; accordingly we examined the rearrangement.

The available information was contradictory, for Inhoffen and Zühlsdorff[7] explained it as an allylic rearrangement in the enols of the 2 : 2-dibromo-ketones, and thus of the intramolecular type, whereas Djerassi and Scholz[16] and Rubin and Hershberg[17] found that it was inhibited by sodium acetate, water, and hydrogen peroxide. These agents are of the kind that inhibit the acid-catalysed bromination of ketones,[18] and the nature of their intervention suggests that the rearrangement is of the intermolecular (pseudo-rearrangement) type,[19] involving debromination and rebromination, which we can explain on the basis of the following displacements:[20]



Our own evidence confirms this contention. In solution in acetic acid containing hydrogen bromide, 2 : 2-dibromocholestan-3-one yields the 2α : 4α-dibromo-compound at a rate proportional to the concentration of the former, and also to that of the hydrogen bromide, which is specific in promoting the change. No rearrangement occurs in refluxing acetic acid or in acetic acid containing perchloric acid or hydrogen chloride; moreover lithium bromide, ascaridole, benzoyl peroxide, or irradiation with ultraviolet light does not initiate it. We could not induce an intramolecular change in conditions that might favour general acid catalysis, *e.g.*, in chlorobenzene containing anhydrous trichloroacetic acid,

[12] Cf. Inhoffen, *Ber.*, 1936, **69**, 2141; Mattox and Kendall, *J. Biol. Chem.*, 1950, **185**, 593; ref. 1.
[13] McBee and Burton, *J. Amer. Chem. Soc.*, 1952, **74**, 3902.
[14] Jones, Ramsay, Herling, and Dobriner, *ibid.*, p. 2828.
[15] Ellis and Petrow, *J.*, 1953, 3869.
[16] Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404; *J. Org. Chem.*, 1948, **13**, 697.
[17] Rubin and Hershberg, quoted by Feiser and Fieser, ref. 5, p. 264.
[18] Cohen, *J. Amer. Chem. Soc.*, 1930, **52**, 2827.
[19] Cf. Dewar, *Ann. Reports*, 1951, **48**, 124.
[20] Cf. Newman, *J. Amer. Chem. Soc.*, 1951, **73**, 4993.

with which, for example, the Orton rearrangement of *N*-acyl-*N*-halogenoanilides can be catalysed.[21] Sodium acetate, added during the rearrangement of the 2 : 2-dibromo-keto-steroid, stops it, but quinol does not interfere.

Therefore, during the acid-catalysed halogenation of 2α-bromocholestan-3-one the immediate product is the *gem.*-dibromide, but as the kinetic control is replaced by the slower adjustments leading to a thermodynamic equilibrium the 2α : 4α-dibromo-ketone takes its place. In this way the steroid rids itself of the more confined axial C–Hal bond, since in the final product both halogens are disposed equatorially to ring A.

The stationary concentration of bromine during the rearrangement is enough hardly to colour the solution. Nevertheless the halogen can be intercepted by β-naphthol, in whose presence the rotation decreases more rapidly than in the straightforward rearrangement, but still at a rate proportional to the concentration of the steroid. The products are 1-bromo-2-naphthol and 2α-bromocholestan-3-one. We infer from these results that the fast debromination of the *gem.*-dibromide is of the first order and that it is succeeded in the rearrangement by the rate-determining bromination at the 4-position, also of the first order with reference to the steroid; the last contention accords with the kinetics of the bromination of ketones.[22] In the absence of hydrogen bromide, β-naphthol had no effect upon a solution of 2 : 2-dibromocholestan-3-one in acetic acid. In mixtures of β-naphthol and 2α-bromocholestan-3-one in acetic acid or carbon tetrachloride the naphthol outstripped the steroid as an absorber of halogen. In the presence of phenol, however, the steroid competed more successfully, so that phenol does not intervene decisively in the rearrangement.

Robinson [23] and Hurst and Macbeth [24] attributed the conversion of α- into γ-bromoacetoacetic ester, in conditions like those in which 2 : 2-dibromo-3-oxo-5α-steroids rearrange, to the transfer of molecular halogen; the literature and the work reviewed herein contain cognate examples.[25] On the other hand, nucleophilic substitutions accompanied by rearrangements also occur in α-halogeno-ketones; [26] this type of rearrangement might be further exemplified in the elimination of hydrogen halides by means of collidine from 2-halogeno-3-oxo-5α-steroids, which affords mixtures of the Δ^1- and Δ^4-3-ketones.[27,28]

Further support for the supposition that the isomerisation of 2 : 2-dihalogeno-3-oxo-5α-steroids involves transfer of molecular halogen comes from the behaviour of the chloro-keto-steroids. Thus 2 : 2-dichlorocholestan-3-one does not rearrange in the presence of hydrogen chloride, and in 2-bromo-2-chlorocholestan-3-one only the bromine atom migrates, apparently under the specific influence of hydrogen bromide.[15,28,29] This behaviour is in accordance with the stability of α-chloro-ketones in these circumstances and with the resistance of α-bromoacetoacetic ester to hydrogen chloride.[30,31] On the other hand α-iodo-ketones are readily dehalogenated, and, as the equilibrium favours this reaction rather than iodination, rearrangement of the halogen substituent is thwarted.[32]

We tried by means of hydrogen bromide in acetic acid to invert the 4-bromo-substituent in 2 : 2 : 4β-tribromocholestan-3-one, but this failed owing to dehalogenation of the steroid; in contrast, perchloric acid in acetic acid caused no noticeable change. If the compound described by Ellis and Petrow [15] as 4-bromo-2 : 2-dichlorocholestan-3-one carries a 4β-substituent, as we suppose, the stability of this axially disposed bromine atom is remarkable,

[21] Bell, *J.*, 1936, 1154; "Acid-Base Catalysis," Oxford Univ. Press, 1941, p. 104.
[22] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, pp. 97, 109, 229; cf. Ralls, *J. Amer. Chem. Soc.*, 1938, **60**, 1744.
[23] Robinson, *Ann. Reports*, 1922, **19**, 100.
[24] Hurst and Macbeth, *J.*, 1922, **121**, 2169.
[25] *E.g.*, Altschul and Bartlett, *J. Org. Chem.*, 1940, **5**, 623; Smith, Wilson, and Woodyer, *Chem. and Ind.*, 1954, 309; cf. Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655.
[26] Eastham, Fisher, Kulka, and Hibbert, *ibid.*, 1944, **66**, 26; Aston *et al.*, *ibid.*, 1951, **73**, 3900, 3902; Stevens and Lenk, *J. Org. Chem.*, 1954, **19**, 538.
[27] Cf. Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003; Fieser and Romero, *ibid.*, 1953, **75**, 4716.
[28] Beereboom and Djerassi, *J. Org. Chem.*, 1954, **19**, 1196.
[29] Beereboom, Djerassi, Ginsburg, and Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 3500.
[30] Cf. Epprecht, *Annalen*, 1894, **278**, 69.
[31] Hantzsch, *Ber.*, 1894, **27**, 355, 3168.
[32] Cf. Pearson and Ross, *J. Amer. Chem. Soc.*, 1952, **74**, 2933.

since the compound survives long treatment in the presence of hydrogen bromide.[33] We presume that the ketone is so encumbered with halogen substituents that enolisation and epimerisation in these conditions are very much hindered.

Experimental

Unless it is stated otherwise, the kinetic experiments were carried out at 25° ± 1°, usually in a 2 dm.-tube shaded from bright lights; anhydrous solvents contained <0·04% (w/v) of water, and the chloroform was alcohol-free. Optical rotations and infrared absorption peaks [34] pertain to solutions of the steroids in $CHCl_3$ and CS_2 respectively, and the m. p.s were taken on a Kofler block.

2 : 2-*Dibromocholestan*-3-*one*.—2α-Bromocholestan-3-one (5 g.) was dissolved in anhydrous acetic acid (360 ml.) at 90° on the steam-bath. A solution of potassium acetate (18·5 g.; dried at 100°) in acetic acid (75 ml.) at 90° was added, followed immediately by 0·619M-bromine in acetic acid (25 ml., 1·42 mol.), added in one lot. Heating was continued on the steam-bath until the bromine colour disappeared (about 12 min. in all). The solution was then cooled as rapidly as possible to room temperature, and set aside for 30 min., during which the product crystallised as white prisms (3·34 g., 57%), m. p. 153—158°, $[\alpha]_D^{22}$ +116° (*c* 0·41), $\nu_{max.}$ 1735 cm.$^{-1}$ (Found: Br, 29·5. Calc. for $C_{27}H_{44}OBr_2$: Br, 29·4%). For this material, made by the acid-catalysed method, Djerassi and Scholz [16] give m. p. 145—147°, $[\alpha]_D^{22}$ +104°. On repeating their method, we obtained a product, m. p. 147—156°, $[\alpha]_D^{23}$ +110° (*c* 1·14). Jones, Ramsey, Herling, and Dobriner [14] give $\nu_{max.}$ 1735 cm.$^{-1}$ for material made by the earlier method.

2 : 2 : 4β-*Tribromocholestan*-3-*one*.—2 : 2-Dibromocholestan-3-one (1 g.) was similarly halogenated with bromine (1·5 mol.) in 0·5N-potassium acetate in acetic acid. The halogen was taken up in 15 min.; addition of water to the cooled solution yielded the white *tribromo-compound* (1·12 g., 98%), m. p. 35—40°, $[\alpha]_D^{20}$ +60° (*c* 0·54), $\nu_{max.}$ 1735 cm.$^{-1}$ (Found: Br, 38·7. $C_{27}H_{43}OBr_3$ requires Br, 38·3%). In spite of its low m. p. and ill-defined absorption in the "fingerprint" region of the infrared spectrum another precipitation from acetic acid did not change its properties. Attempts at crystallising this compound led to its decomposition.

A solution of the above tribromo-compound in 0·04N-hydrogen bromide in anhydrous acetic acid displayed a rapidly diminishing rotation, which stopped changing after 30 min. Isolation of the steroidal product by the addition of water and subsequent crystallisation from hexane yielded 2α : 4α-dibromocholestan-3-one, m. p. 186—189°, $[\alpha]_D^{20}$ −3° (*c* 0·43), $\nu_{max.}$ 1756 cm.$^{-1}$, which was finally identified by a mixed m. p. determination with authentic material and a comparison of the infrared spectra of the two specimens. Wilds and Djerassi,[35] and Jones *et al.*,[14] give m. p. 194°, $[\alpha]_D$ +3°, $\nu_{max.}$ 1756 cm.$^{-1}$. In the least quantity of 0·1N-hydrogen bromide in acetic acid a greater change in rotation occurred; addition of water precipitated a crude solid, m. p. 61—73°, $[\alpha]_D^{20}$ −33° (*c* 0·38), $\nu_{max.}$ 1706 and 1756 cm.$^{-1}$ (*ca.* equal intensity), that resembled the product (Found: Br, 29·9%) from the attempted acid-catalysed dibromination of 2α-bromocholestan-3-one. It must contain a hitherto unknown bromocholestan-3-one, since all the known members of this series have much higher rotations. Polarimetric evidence disclosed little change in the 2 : 2 : 4β-tribromo-compound dissolved in anhydrous 0·09N-perchloric acid in acetic acid.

Rearrangement of 2 : 2-*Dibromocholestan*-3-*one with Hydrogen Bromide as Catalyst*.—In each experiment in this series 2 : 2-dibromocholestanone (100 mg.) was dissolved in anhydrous acetic acid (20 ml.), and the rotation of the cooled solution measured. The required amount of 0·6N-hydrogen bromide in acetic acid was added, and the rotation observed at suitable intervals, corrections being made for the addition of the catalyst solution. The values of the velocity constants *k* were calculated from the equation for a first-order reaction:

$$k = [2{\cdot}303/(t_y - t_x)][\log_{10}(A_x - A_\infty) - \log_{10}(A_y - A_\infty)]$$

where A_x, A_y, and A_∞ are respectively the rotations after *x* and *y* minutes and at the end of the change. The values of *k* for different concentrations of hydrogen bromide are tabulated.

Normality of HBr	0·02	0·03	0·04	0·05	0·10
k_{mean} (min.$^{-1}$)	0·026	0·046	0·057	0·080	0·167
Standard deviation	±0·003	±0·007	±0·010	±0·024	±0·018
k_{mean}/[HBr]	1·3	1·5	1·4	1·6	1·7

[33] Cf. ref. 4.
[34] Cf. Dickson, Page, and Rogers, *J.*, 1955, 443.
[35] Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1712.

Rearrangement of 2 : 2-*Dibromocholestan*-3-*one in the Presence of* β-*Naphthol.*—Two small-scale (100 mg.) experiments were performed in a similar manner to the rearrangements previously described with 0·04N-hydrobromic acid solution, except that in the first 5 mol. and in the second 1·1 mol. of β-naphthol were present. In each the rotation (corrected to 20 ml. of solution) dropped from α_D +1·10° to +0·43° in 20 min., whereas the final rotation in the absence of β-naphthol was +0·04°. The changes obeyed first-order kinetics, where $k_{mean} = 0·379 (\pm 0·082)$ min.$^{-1}$. This value was obtained at 23°.

On a larger scale, 2 : 2-dibromocholestan-3-one (933 mg.) was dissolved in warm anhydrous acetic acid (100 ml.) and cooled, and β-naphthol (purified; 1·0 mol., 247 mg.) was added and dissolved. Finally 0·6N-hydrogen bromide in acetic acid (7·0 ml.) was added, and the solution kept in the dark for 75 min. It was then poured into water, and the acid neutralised with the calculated amount of sodium hydrogen carbonate. The mixture was extracted with ether (3 × 100 ml.), and the ether extracted with N-sodium hydroxide (8 × 25 ml.). The alkaline extracts were acidified with hydrochloric acid, and the precipitated bromonaphthol was extracted with ether (3 × 50 ml.), and recovered by evaporation of the washed extract, which yielded it as a gum (356 mg., 89%). Crystallisation from hexane gave brown crystals (228 mg.), some of which were sublimed at 60—70°/10^{-1} mm. to form white 1-bromo-2-naphthol, m. p. 81° (capillary tube). The recorded m. p.[36] varies from 81° to 84°.

The original ether extract, containing neutral material, was washed three times with water, dried ($MgSO_4$), and evaporated. The crude product (790 mg., 100%) had $[\alpha]_D^{26}$ +38° (*c* 0·60). This was crystallised from ethanol–acetone (5 : 1), to yield needles (520 mg.) of 2α-bromocholestan-3-one, m. p. 164—169°, $[\alpha]_D^{26}$ +45° (*c*, 0·54), $\nu_{max.}$ 1730 cm.$^{-1}$ (Found : Br, 16·4. Calc. for $C_{27}H_{45}OBr$: Br, 17·2%). This material was identified by its infrared spectrum and by a mixed m. p. with authentic material (lit.,[14, 37] m. p. 168—169°, $[\alpha]_D$ +42°, $\nu_{max.}$ 1733 cm.$^{-1}$).

The rotation of a solution of 2 : 2-dibromocholestan-3-one in acetic acid was unchanged by the addition of β-naphthol when hydrogen bromide was absent.

Competitive Bromination Experiments.—In each of these experiments the steroid (0·10 g.) was dissolved in an anhydrous solvent (10 ml.) to which the phenolic competitors were added in equimolecular proportions with the steroid. No change in rotation was noticed when solutions of 2α-bromo- or 2 : 2-dibromo-cholestan-3-one were treated with such competitors. In series *A* cholestan-3-one was halogenated alone and in the presence of phenol and β-naphthol with bromine (2 mol.) in chloroform–acetic acid (1 : 1). In series *B* carbon tetrachloride was used as solvent instead of the mixture used in series *A*. In series *C* 2α-bromocholestan-3-one was halogenated with bromine (1 mol.) in the chloroform–acetic acid mixture, with and without competitors. The concentration of hydrogen bromide (generated by the halogenation) in series *A* and *B* was *ca.* 0·025N, whereas in series *C* it was 0·013N. The rotations of the solutions at differing times are given in the Table.

*Competitive brominations.**

	Experiment and nature of competitor	Initial rotation	Maximum rotation † (α_{max})	Time † to reach max. (min.)	Steady rotation (α)	Time to reach final val. (approx.) (min.)
A	None	0·49°	0·80°	10	0·11°	300
	Phenol	0·49	0·68	5	0·32	120
	β-Naphthol	0·49	0·56	10	0·41	180
B	None	0·46	0·86	5	0·11	300
	Phenol	0·46	0·75	5	0·57	420
	β-Naphthol	0·46	None	—	0·50	10
C	None	0·59	0·88	20	0·18	420
	Phenol	0·59	0·73	5	0·56	60
	β-Naphthol	0·59	0·65	10	0·60	300

* All rotations positive. † Approximate, as the rotation alters very quickly in the early stages.

Other Attempts to catalyse the Rearrangement.—The following agents had no effect (judged polarimetrically) on anhydrous 0·5% (w/v) solutions of 2 : 2-dibromocholestan-3-one in anhydrous acetic acid : perchloric acid or hydrogen chloride (final concentration 0·04N); anhydrous lithium bromide (which had a final concentration of *ca.* 0·03N and even at 100°

[36] *E.g.*, Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 245; Hazlet, *J. Amer. Chem. Soc.*, 1940, **62**, 2156; ref. 2.
[37] Fieser and Dominguez, *ibid.*, 1953, **75**, 1705.

initiated no change); benzoyl peroxide. Irradiation of such solutions with ultraviolet light was ineffectual. Addition of benzoyl peroxide or quinol did not affect the going rearrangement, promoted with hydrogen bromide. A commercial sample of ascaridole stopped it. Treatment of a solution of 2 : 2-dibromocholestan-3-one in anhydrous chlorobenzene with anhydrous trichloroacetic acid in the same solvent (acid finally 0·03N) initiated no change, even when the solution was warmed.

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838. *Studies in the Synthesis of Cortisone. Part XVIII.* The Preparation of Cortisone Esters from 4 : 5α-Dihydrocortisone.*

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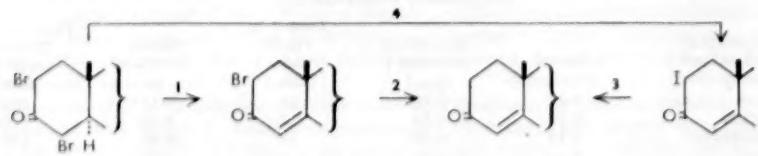
A study of the bromination of 4 : 5α-dihydrocortisone acetate led to isolation of a crystalline 2 : 4-dibromo-derivative, which was converted into cortisone 21-acetate and 17 : 21-diacetate by two different routes. The first proceeds *via* the reaction (first described by Djerassi) of the dibromo-steroid with sodium iodide and bromoacetone in acetone, and a new method using Girard reagents for the separation of cortisone mono- or di-acetate from the by-products of the reaction is described. The alternative route is based on the preferential reduction of 2 : 4-dibromo-3-oxo-5α-steroids to the hitherto unknown 4-bromo-3-oxo-5α-steroids, which are readily converted into the corresponding 3-oxo-Δ^4-steroids.

THE difficulty of introducing a 4 : 5-double bond into 3-oxo-5α-steroids has to a great extent precluded the use of sterols and sapogenins of this series as starting materials for preparation of the adrenal hormones. The derivation of the essential 3-oxo-Δ^4-system from 2 : 4-dibromo-3-oxo-5α-steroids was first described by Inhoffen and Zühlsdorff;[1] it is also formed, together with the Δ^1-isomer, during the dehydrohalogenation of 2-bromo-3-oxo-5α-steroids by bases.[2]

Inhoffen and Zühlsdorff's method,[1] which involves partial dehydrobromination of the 2 : 4-dibromo-3-oxo-5α-steroid (I) and reduction of the resulting unsaturated monobromo-ketone (II), was later improved by Rosenkranz *et al.*,[3] who showed that the dibromo-ketone (I) with sodium iodide in acetone under reflux gave a 2-iodo-3-oxo-Δ^4-steroid (IV); this, like the bromo-analogue (II), could be readily reduced to the 3-oxo-Δ^4-steroid (III).



(I) (II) (III) (IV)

Reagents: 1, collidine; 2, Zn,AcOH; 3, HI or $CrCl_2$ or Zn,AcOH; 4, NaI.

The improved method has been widely used for preparation of Δ^4-3-ketones with stable side chains and lacking a substituent at $C_{(11)}$, but was less efficient in the preparation of adrenal hormones (cf. refs. 4 & 5).

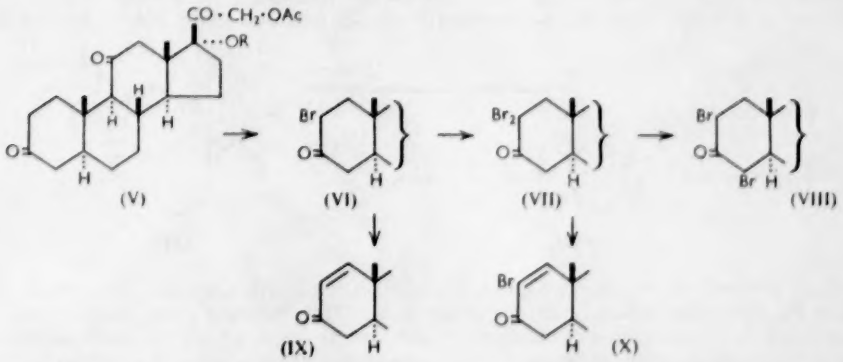
* Part XVII, preceding paper.

[1] Inhoffen and Zühlsdorff, *Ber.*, 1943, **76**, 2351.
[2] Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404; Beereboom and Djerassi, *J. Org. Chem.*, 1954, **19**, 1196.
[3] Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077.
[4] Rosenkranz, Pataki, St. Kaufmann, Berlin, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4081; Sondheimer, Rosenkranz, Mancera, and Djerassi, *ibid.*, 1953, **75**, 2601.
[5] Rosenkranz, Djerassi, Yashin, and Pataki, *Nature*, 1951, **168**, 28.

By following the method of Sondheimer, Rosenkranz, Mancera, and Djerassi [4] for conversion of 4 : 5α-dihydrocortisone acetate (V; R = H) into cortisone acetate (XII; R = H), we were unable to obtain an overall yield of more than 10% and experienced great difficulty in separating the reaction products, the starting material being the major contaminant. Observation (by ultraviolet absorption and precipitation of sodium bromide) of the rates of formation of the αβ-unsaturated ketone system during the reaction of the crude dibromo-ketone (VIII; R = H) with sodium iodide in acetone, revealed wide variations and led us to suspect the purity of the bromo-steroid. Attempts to purify this intermediate by chromatography on alumina led to a marked loss of halogen and on several occasions a small quantity of a diacetate, later identified as (VI; R = Ac), was isolated. Since the dibromo-ketone (VIII; R = H) was common to other projected routes for the conversion of the dihydro-acetate (V; R = H) into cortisone acetate (XII; R = H), we made a detailed study of its preparation.

Monobromination of the triketone (V; R = H) in acetic acid [6,7] gave the compound (VI; R = H) but, contrary to the observations of Oliveto *et al.*,[7] we found that dehydrobromination *via* the semicarbazone proceeded smoothly to the Δ^1-ketone (IX; R = H) (there are notable differences in the records of physical properties for this compound [6,8] and our observations do not completely confirm any of the records). Dehydrobromination of the bromo-ketone (VI; R = H) by collidine may lead to contamination of the product with the corresponding Δ^4-3-ketone (cf. Djerassi *et al.*[2]).

Attempted free-radical bromination of the monobromo-ketone (VI; R = H), by means of *N*-bromosuccinimide in allyl bromide with the addition of benzoyl peroxide or on irradiation,[9] failed to yield the 2 : 2-dibromo-ketone (VII; R = H), and acid-catalysed bromination was unsuccessful. However, as with 2-bromocholestan-3-one (see preceding paper), base-catalysed bromination gave the 2 : 2-dibromo-compound (VII) smoothly and its structure was confirmed by carefully controlled dehydrobromination in collidine to the bromo-Δ^1-3-ketone (X; R = H).



Polarimetric studies showed that the rearrangement (VII; R = H) ⟶ (VIII; R = H) catalysed by hydrogen bromide was complete within 15—30 minutes, in contrast to the 16 hours allowed by Rosenkranz, Djerassi, Yashin, and Pataki,[5] also that in a number of media the rearrangement was a first-order reaction with reference to the ketone (VII; R = H) (see p. 4362). Experiments on a larger-scale gave the crystalline 2 : 4-dibromo-ketone (VIII; R = H), which, unlike the product obtained in our earlier experiments, was stable and homogeneous when chromatographed on alumina. However, a slow change occurred in acetic acid containing hydrogen bromide, the α_D of the solution decreasing steadily. This might be accounted for in part by acetylation of the

[6] Wilson and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 1609.
[7] Oliveto, Gerold, and Hershberg, *ibid.*, p. 2248.
[8] Kendall and Mattox, U.S.P. 2,590,978; Kaufmann and Pataki, *Experientia*, 1951, **7**, 260.
[9] Djerassi and Scholz, *ibid.*, 1947, **3**, 107; Hare and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 891.

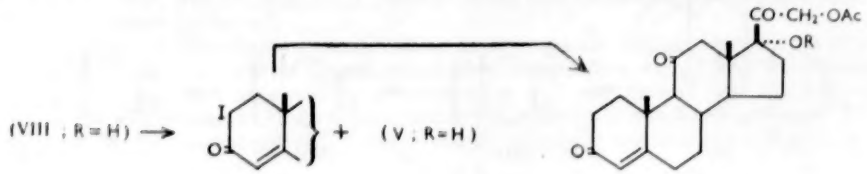
17α-hydroxy-group, since the acetate (VI; R = Ac) had already been isolated from the crude dibromo-ketone.

Our new evidence on the rearrangement and probable side reactions proved that the time taken in the direct preparation of the 2 : 4-dibromo-ketone (VIII; R = H) from dihydrocortisone acetate (V; R = H) had been excessive. In acetic acid containing hydrogen bromide (1·0N), the first mol. of bromine was absorbed instantaneously and the second in 3—5 minutes. The optical rotation of the solution became steady after a further 15 minutes and isolation of the products at this point gave crystalline 2 : 4-dibromo-ketone (VIII; R = H).

The reaction of this crystalline 2 : 4-dibromo-ketone (VIII; R = H) with sodium iodide in boiling acetone seemed to be complete within three hours. At high dilutions an induction period of 30—60 minutes occurred, but was avoided by adding a trace of mineral acid. Lithium iodide in place of sodium iodide gave similar results and no solvent was found to be superior to acetone.

The appearance of iodine during the reaction and the presence of saturated keto-steroids amongst the reaction products indicated reduction of the intermediate halogeno-steroids by hydrogen iodide. Separate experiments showed that hydrogen iodide in acetone readily reduced the dibromo-ketone (VIII; R = H) and that the reduction of the Δ^4-bond in the αβ-unsaturated ketones could not be held responsible for the low ultraviolet absorption of the products (cf. Fried and Sabo [10]). Attempts to remove the hydrogen iodide by the addition of inorganic or organic bases or epoxides served only to retard or inhibit the reaction, but favourable results were obtained by the inclusion of a second α-iodo-ketone, *e.g.*, iodoacetone, to react competitively with the hydrogen iodide, but the addition of large amounts of it did not completely prevent the formation of saturated keto-steroids.

The 2-iodo-steroid (XI; R = H), being too unstable for isolation in the pure state, was converted by controlled dehalogenation into crude cortisone acetate by hydrogen iodide generated *in situ*. Chromous chloride, or zinc and acetic acid, could also be used in the presence of sodium iodide though they reduced the Δ^4-bond. The halogen-free product isolated at this stage consisted predominantly of cortisone 21-acetate, but, in spite of the



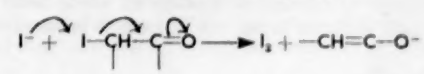
(XI) (XII)

use of iodoacetone in the foregoing reaction, 4 : 5α-dihydrocortisone 21-acetate (V; R = H) still appeared in appreciable amounts. This mixture could not be readily separated by crystallisation or chromatography, but Anchel and Schoenheimer's method [11] with the carboxyphenylhydrazones was successful, although some destruction of the steroids occurred during formation of the derivatives. A greatly improved method was found, however, by use of formaldehyde for the selective decomposition of the Girard P and T [12] derivatives : at pH 7 the saturated ketone (V; R = H) was liberated, whereas cortisone acetate (XII; R = H) was regenerated only at pH 1. The fraction obtained at pH 7 (formaldehyde–acetic acid–alcohol) was contaminated with αβ-unsaturated ketones, probably cortisone acetate and compounds with Δ^1-3-oxo-, $\Delta^{1:4}$-3-oxo-, and $\Delta^{8(9)}$-11-oxo-chromophores. Compounds of the last-mentioned type presumably arose from the corresponding 9α-bromo-steroids.[13] Further separation of this mixture was not practicable, but it was reduced catalytically to give some 4 : 5α-dihydrocortisone

[10] Fried and Sabo, *J. Amer. Chem. Soc.*, 1953, **75**, 2273.
[11] Anchel and Schoenheimer, *J. Biol. Chem.*, 1936, **114**, 539.
[12] Reichstein, *Helv. Chim. Acta*, 1935, **19**, 1107.
[13] Crawshaw, Henbest, Jones, and Wagland, *J.*, 1955, 3420.

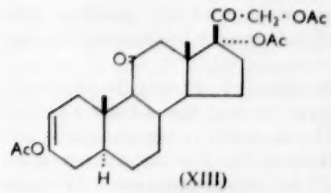
21-acetate (V; R = H). Crystallisation of the fraction from the Girard derivatives that decomposed at pH 1 yielded pure cortisone 21-acetate.

The fact that iodoacetone did not completely prevent the formation of 4 : 5α-dihydrocortisone acetate (V; R = H) may, perhaps, be explained by assuming that the iodide ion itself may act as a reducing agent in the following way :



A precedent for this mechanism is set by the action of sodium iodide on the toluene-*p*-sulphonyl esters of certain α-glycols : [14]

In the earlier phases of these investigations we had thought that the low yields of cortisone acetate (XII; R = H) might be accounted for by the destruction of the cortical side chain during the reactions necessary for introducing the double bond and that such difficulties might be overcome by esterification of the 17α-hydroxyl group. We therefore investigated the reactions with the corresponding 17α : 21-diacetates. The preparation of 17α-acetates with acetic anhydride alone or with acid catalysts has been described by Turner and others,[15] and we found that in a like manner the reaction between acetic anhydride and dihydrocortisone acetate (V; R = H) in benzene [16] catalysed by perchloric acid gave 3β : 17α : 21-triacetoxy-5α-pregn-2-ene-11 : 20-dione (XIII) in high yield. The position of the double bond was in accord with earlier observations,[17] as shown by bromination in acetic acid to the 2-bromo-ketone (VI; R = Ac), and was confirmed by alkaline hydrolysis, with subsequent acetylation, to dihydrocortisone monoacetate (V; R = H), whereas acid hydrolysis with subsequent acetylation gave the diacetate (V; R = Ac). [The physical properties recorded by Huang-Minlon, Wilson, Wendler, and Tishler[15b] for the diacetate, which they obtained by acetylation of the monoacetate catalysed by toluene-*p*-sulphonic acid, did not agree with those of our material, but were identical with those we obtained for the unsaturated triacetate (XIII) : repetition of their experiment gave in fact the latter product.]



(XIII)

Further bromination of the 2-bromo-ketone (VI; R = Ac) in acetic acid containing sodium acetate at 70° gave the 2 : 2-dibromo-ketone (VII; R = Ac), which rearranged under the influence of hydrogen bromide in chloroform to the 2 : 4-dibromo-ketone (VIII; R = Ac). This compound, however, was prepared more conveniently from the Δ^2-triacetate (XIII) by 2 mols. of bromine in chloroform, as described for the corresponding 17α-hydroxy-compound. Treatment of the dibromo-ketone (VIII; R = Ac) with sodium iodide in the presence of iodoacetone in refluxing acetone, de-iodination, and separation of the products gave cortisone diacetate (XII; R = Ac).

Acid hydrolysis of the esters (V and XII; R = Ac) removed only the 21-acetoxy-groups, but methanolic sodium hydroxide or methoxide gave the corresponding 17α : 21-diols. The amount of alkali was found to be critical : more than 2 equivalents caused destruction of the side chain, and only 1 equivalent was necessary for complete hydrolysis.*

* Similar observations have recently been made on Reichstein's substance S by Reingold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 820.

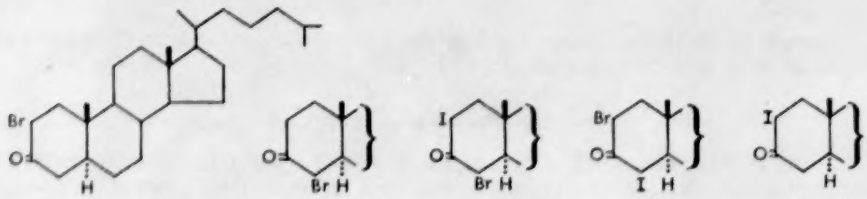
[14] Foster and Overend, *J.*, 1951, 3452; Newth, *J.*, 1956, 471.

[15] (*a*) Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 4220; 1953, **75**, 3489; Moffett and Anderson, *ibid.*, 1954, **76**, 5394; Oliveto, Gerold, Weber, Jorgensen, Raussar, and Hershberg, *ibid.*, 1953, **75**, 5486; (*b*) Huang-Minlon, Wilson, Wendler, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 5394.

[16] Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747.

[17] Inhoffen, Becker, and Kölling, *Annalen*, 1950, **576**, 181; Rubin and Armbrecht, *J. Amer. Chem. Soc.*, 1953, **75**, 3513.

The efficient formation of 3-oxo-Δ^4-steroids from the corresponding 4-bromo-3-oxo-5β-steroids [18, 19] led us to investigate the preparation of the hitherto unknown 4-bromo-3-oxo-5α-steroids, with a view to finding an alternative route to cortisone acetate from the 2 : 4-dibromo-ketone (VIII; R = H). Preliminary attempts to hydrogenolise preferentially the 2-bromine atom in 2 : 4-dibromocholestan-3-one with a palladium catalyst failed. With the theoretical amount of chromous acetate in acetic acid a monobromo-ketone (XV*a*) was obtained, which differed from the known 2-bromo-compound (XIV). The

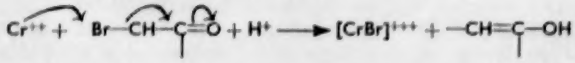


(XIV) (XV) (XVI) (XVII) (XVIII)

Series (*a*) : cholestanone type.
,, (*b*) : 4 : 5α-dihydrocortisone 21-acetate type.

4-position of the bromine atom was established by conversion of the product into cholest-4-en-3-one on treatment with semicarbazide [19] and subsequent hydrolysis [20] of the 3-semicarbazonocholest-4-ene.

Carefully controlled reductions of 21-acetoxy-2 : 4-dibromo-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (VIII; R = H) with chromous salts gave mainly the 4-bromo-ketone (XV*b*), which was converted into cortisone 21-acetate (XII; R = H) by the semicarbazide procedure.[18] The by-products of these reductions contained the 2-bromo-isomer from which 4 : 5α-dihydrocortisone acetate could be recovered by dehalogenation. Titanous sulphate was slightly less effective in producing the 4-bromo-ketone (XV*b*), and the use of halogen acceptors such as phenol and β-naphthol (cf. preceding paper) gave mixtures of bromo-ketones. We suggest that the reducing cation may act thus :



Acid-catalysed halogenation of 4-bromocholestanone (XV*a*) and 4-bromo-4 : 5α-dihydrocortisone 21-acetate (XV*b*) proceeded smoothly with bromine or iodine monochloride, giving the corresponding 2 : 4-dihalogeno-steroids. The 2 : 4-dibromocholestan-3-one so obtained was identical with that prepared by acid-catalysed bromination of cholestan-3-one, but the dibromo-ketone obtained from the Δ^4-ketone (III*b*) had a specific rotation lower than that of the product resulting from the direct bromination of the saturated ketone (V; R = H).

In contrast to the behaviour of 2-bromo-3-oxo-5α-steroids, replacement of the bromine atom in the 4-bromo-3-oxo-5α-steroids by means of sodium iodide does not occur in acetone at room temperature or on boiling, and was very slow in boiling ethyl methyl ketone. This behaviour resembles that of 4-bromo-3-oxo-5β-steroids [21] and emphasises the great reactivity of both bromine atoms in 2 : 4-dibromo-3-oxo-5α-steroids. Attempts to prepare the 4-bromo-2-iodosteroids (XVI*a* and *b*) by reaction of the 2 : 4-dibromo-5α-steroids with sodium iodide in acetone [3] at 20° were unsuccessful, and de-iodination of the crude products by sodium metabisulphite gave mixtures of 2- and 4-bromo-ketones. The bromoiodo-ketone so prepared differed from that prepared from (XV*a*) by reaction with iodine monochloride.

The difference in reactivities of 2- and 4-bromine atoms in 5α-steroids was used as the basis

[18] McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5811.
[19] Holysz, *ibid.*, 1953, **75**, 4432.
[20] Hershberg, *J. Org. Chem.*, 1948, **13**, 542.
[21] Julian and Karpel, *J. Amer. Chem. Soc.*, 1950, **72**, 362.

of a modified preparation of cortisone acetate. The crude product obtained as above by chromous chloride reduction of the 2 : 4-dibromo-compound (VIII; R = H) was refluxed with sodium iodide in acetone, and the resulting mixture of 2-iodo- (XVIII*b*) and 4-bromo-3-oxo-5α-steroids (XV*b*) was reduced by sodium hydrogen sulphite or titanous chloride (both of which preferentially reduce the 2-iodine atom), or with the calculated quantity of chromous chloride solution. The product, which then consisted of 4 : 5α-dihydrocortisone 21-acetate and the 4-bromo-ketone (XV*b*), was treated with semicarbazide, the semicarbazones were hydrolysed, and the resulting mixture was separated by Girard P reagent, as described earlier.

	ΔM_D
2-Bromination.	
Cholestan-3-one ⟶ 2-bromocholestan-3-one (XIV)	+ 28°
4 : 5α-Dihydrocortisone acetate (V) ⟶ (VI)	+214
2 : 4-Dibromination.	
Cholestan-3-one ⟶ 2 : 4-dibromocholestan-3-one	−142
4 : 5α-Dihydrocortisone acetate (V) ⟶ (VIII)	+ 63
4-Bromination.	
Cholestan-3-one ⟶ 4-bromocholestan-3-one (XVI*a*)	−159
4 : 5α-Dihydrocortisone acetate (V) ⟶ (XV*b*)	−156

The equatorially disposed C–Br bonds of 2- and 4-bromocholestanone cause characteristic shifts of the ketone absorption,[22] whereas it is not possible to observe changes in the ultraviolet and infrared absorption of the polyketones under discussion which might be due to the differing orientation of 2- and 4-bromine atoms. We have not attributed configurations to the bromine atoms in the derivatives of 4 : 5α-dihydrocortisone acetate because the compounds, although made by the usual methods, show irregularities in the molecular-rotation differences accompanying their formation. From 2-bromination there is a greater rotational increase in 4 : 5α-dihydrocortisone acetate than in cholestan-3-one, and the difference is still present in the 2 : 4-dibromo-compounds, the effect of 4-bromination being nearly the same in both instances (see Table). The large rotational increment on 2-bromination of 4 : 5α-dihydrocortisone acetate may indicate a different 2-bromo-configuration in 11-oxo-steroids. Bromination of 4-bromo-4 : 5α-dihydrocortisone acetate gave a product with a specific rotation 10° lower than that of the 2 : 4-dibromo-ketone obtained from the 2-bromo-compound. The $[\alpha]_D$ rose 7° on equilibration in acetone with lithium bromide and therefore the 2 : 4-dibromo-compound could contain variable proportions of 2α- and 2β-epimers.

Experimental

Solvents (except when otherwise stated) were $CHCl_3$ for optical rotations (concn. limits 0·5—1·5%), EtOH for ultraviolet absorption spectra, and bromoform for infrared spectra.* The infrared spectra were recorded on a Perkin–Elmer Model 21 double-beam spectrophotometer fitted with sodium chloride optics, and the assignments are based on those summarised by Jones and Herling.[23]

4 : 5α-*Dihydrocortisone* 21-*Acetate* (V; R = H).—This was prepared from 3β-acetoxy-17α-hydroxy-5α-pregnane-11 : 20-dione[25] by the method described by Pataki, Rosenkranz, and Djerassi,[26] except that *tert.*-butyl alcohol and pyridine were used as solvent for the oxidation. Chromatography and crystallisation from acetone and benzene gave prisms, m. p. 231—236° (sintering at temperatures above 200°), $[\alpha]_D^{26}$ +103° (*c* 0·6), +89° (*c* 0·2 in acetone), $\lambda_{max.}$ 295 mμ

* Bromoform [24] has a great advantage over chloroform as a solvent for the infrared study of compounds that are insoluble in carbon disulphide and carbon tetrachloride, since in addition to transmitting in the C=O stretching region (1800—1600 cm.$^{-1}$), it transmits in the C–O stretching region (1270—1200 cm.$^{-1}$), and permits the acetate C–O band to be identified. However, Nujol transmits over a wider spectral region than bromoform.

[22] Jones, Ramsey, Herling, and Dobriner, *ibid.*, 1952, **74**, 2828; Jones, *ibid.*, 1953, **75**, 4839; Corey, *ibid.*, p. 4832; Fieser and Huang, *ibid.*, p. 4837.
[23] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.
[24] Tarpley and Vitiello, *Analyt. Chem.*, 1952, **24**, 315.
[25] Cf. ref. 16.
[26] Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615.

(ε 249; *c* 0·004), $\nu_{max.}$ 1743 and 1231 (21-OAc), 1725 (20-CO), and 1704 cm.$^{-1}$ (3- and 11-CO) (Found: C, 68·4; H, 7·9. Calc. for $C_{23}H_{32}O_6$: C, 68·3; H, 8·0%). These properties differ from those given in the literature.[6, 7, 26, 27]

21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VI; R = H).—Bromine (8·3 g., 1·05 mol.) in acetic acid (100 ml.) was added to a stirred solution of 4 : 5α-dihydrocortisone acetate (V; R = H) (20 g.) in acetic acid (2·5 l.) containing a trace of hydrogen bromide. After the bromine was taken up, water was added and the steroid extracted into chloroform. The residue, evaporated under reduced pressure, crystallised from ethyl acetate as needles of the solvated 2-bromo-ketone (VI; R = H) (18 g., 64%), m. p. 185—192° (decomp.), $[\alpha]_D^{20}$ +110°, $\lambda_{max.}$ 207 and 292 mμ (ε 2320 and 131 respectively), $\nu_{max.}$ 1745 and 1232 (21-OAc), 1727 (20-CO) and 1708 cm.$^{-1}$ (CO) (Found: Br, 14·7. Calc. for $C_{23}H_{31}O_6Br,CH_3{\cdot}CO_2C_2H_5$: Br, 14·0%). Wilson and Tishler [6] give m. p. 179—185° (decomp.), $[\alpha]_D^{24}$ +102°. The product was eluted quantitatively by benzene from an alumina column. It formed also a benzene solvate, m. p. 182—192° (decomp.), $[\alpha]_D^{20}$ +112° (Found: C, 59·6; H, 6·45; Br, 14·8. Calc. for $C_{23}H_{31}O_6Br,\frac{1}{4}C_6H_6$: C, 59·8; H, 6·5; Br, 15·3%), and an acetone solvate, m. p. 187—189° (decomp.), $[\alpha]_D^{23}$ +116° (Found: C, 57·9; H, 6·5; Br, 14·6. Calc. for $C_{23}H_{31}O_6Br,C_3H_6O$: C, 57·7; H, 6·9; Br, 14·8%).

21-*Acetoxy*-17α-*hydroxy*-5α-*pregn*-1-*ene*-3 : 11 : 20-*trione* (IX; R = H).—2-Bromo-4 : 5α-dihydrocortisone acetate (VI; R = H) (14 g.; ethyl acetate solvate) in dry alcohol-free chloroform (240 ml.) and *tert.*-butyl alcohol (320 ml.) was shaken under carbon dioxide with finely powdered semicarbazide (3·2 g.) for 30 min. The residue, after removal of the solvents under reduced pressure, was triturated with ethanol (152 ml.) and then water (104 ml.), and filtered. The washed, wet solid was suspended in acetic acid (265 ml.), water (95 ml.), and 1·13N-aqueous pyruvic acid (34 ml.) and heated at 75° for 30 min. The solution was diluted with hot water and kept at room temperature overnight; the Δ^1-3-ketone (IX; R = H) crystallised as needles (6·5 g., 67%), m. p. 250—252° (decomp.), $[\alpha]_D^{24}$ +129°, +118° (in acetone), $\lambda_{max.}$ 227 mμ (ε 11,700), $\nu_{max.}$ 1745 and 1228 (21-OAc), 1725 (20-CO), 1704 (CO), 1668, 1600, and 780 cm.$^{-1}$ (α : β-unsaturated ketone) (Found: C, 68·5; H, 7·6. Calc. for $C_{23}H_{30}O_6$: C, 68·6; H, 7·5%). Recorded data [6, 7, 8] are divergent. The 3-(2 : 4-dinitrophenylhydrazone) had m. p. 240—242°, $\lambda_{max.}$ 385 mμ (ε 34,700 in $CHCl_3$) (Found: N, 9·6. Calc. for $C_{29}H_{34}O_9N_4$: N, 9·6%); Wilson and Tishler [6] give $\lambda_{max.}$ 375 mμ (log ε 4·45 in MeOH) for the unpurified hydrazone.

21-*Acetoxy*-2 : 2-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VII; R = H).—Bromine (3·22 g., 1·15 mol.) in 0·5N-potassium acetate solution in acetic acid (100 ml.) was added to 21-acetoxy-2-bromo-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (VI; R = H) (10 g.; ethyl acetate solvate) in 0·5N-potassium acetate solution in acetic acid (500 ml.). The solution was heated on a steam-bath until the colour had disappeared (15 min.) and then poured into brine (*ca.* 10 l.). The precipitated white solid was collected, washed, and dried (10 g.; $[\alpha]_D^{20}$ +138°). Crystallisation from ethyl acetate–*n*-hexane yielded rhombs of the 2 : 2-*dibromo-ketone* (VII; R = H) (4·25 g., 44%), m. p. 160—164° (decomp.), $[\alpha]_D^{20}$ +152°. Recrystallisation from ethyl acetate–*n*-hexane gave rhombs, m. p. 160—166° (decomp.), $[\alpha]_D^{19}$ +151°, $\lambda_{max.}$ 206 mμ (ε 3710) (at 292 mμ ε was 422), $\nu_{max.}$ 1748 and 1230 (21-OAc), 1725 (20-CO), and 1707 cm.$^{-1}$ (CO) (Found: C, 49·4; H, 5·5; Br, 28·1. $C_{23}H_{30}O_6Br_2$ requires C, 49·1; H, 5·3; Br, 28·4%).

21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregn*-1-*ene*-3 : 11 : 20-*trione* (X; R = H).—2 : 2-Dibromo-4 : 5α-dihydrocortisone acetate (4 g.) was added to boiling *sym.*-collidine (20 ml.; redistilled), and the mixture refluxed for 2 min., rapidly cooled to room temperature, and diluted with benzene (50 ml.). Extraction of the collidine with 2N-hydrochloric acid (4 × 50 ml.), washing of the benzene solution with aqueous sodium hydrogen carbonate and water, and evaporation yielded a residue (3·1 g.) which was chromatographed on alumina. Benzene eluted a solid (1·66 g.), crystallising from methanol as rods of the 2-*bromo*-Δ^1-*ketone* (X; R = H) (1·28 g., 39%), m. p. 200—201° (decomp.), $[\alpha]_D^{20}$ +119°, +102° (in acetone), $\lambda_{max.}$ 255 mμ (ε 7500), $\nu_{max.}$ 1745 and 1230 (21-OAc), 1725 (20-CO), 1704 (CO), 1688 and 1595 cm.$^{-1}$ (αβ-unsaturated α-bromo-ketone) (Found: C, 57·2; H, 6·1; Br, 16·5. $C_{23}H_{29}O_6Br$ requires C, 57·4; H, 6·1; Br, 16·6%).

Polarimetric Study of the Rearrangement of the 2 : 2- (VII; R = H) *to the* 2 : 4-*Dibromo-compound* (VIII; R = H).—The 2 : 2-dibromo-compound (VII; R = H) (100 mg.) was dissolved in anhydrous solvents (25 ml.) made 0·8N with respect to hydrogen bromide, and the rotations of the solutions were taken at suitable intervals. The temperature variations were

[27] Djerassi, Rosenkranz, Pataki, and Kaufmann, *J. Biol. Chem.*, 1952, **194**, 115.

$\pm 1°$, and all the experiments were undertaken within the range $20° \pm 2°$. The results are as follows, each set being in the order $t_{0.5}$ (min.), k (min.$^{-1}$), and σ: acetic acid, 1·5, 0·396, ± 0·069; benzene, 11, 0·033, ± 0·004; chloroform, 29, 0·021, ± 0·001; dioxan, 8, 0·09, ± 0·001; ethyl acetate, 3, 0·233, ± 0·018; ethyl bromide, 3, 0·125, ± 0·018; methylene dichloride, 7, 0·091, ± 0·004; nitromethane, 8, 0·090, ± 0·008.

21-*Acetoxy*-2 : 4-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = H) *from the* 2 : 2-*Dibromo-ketone* (VII; R = H).—The 2 : 2-dibromo-ketone (VII; R = H) (1·2 g.) in acetic acid (250 ml.) was treated with 3·4N-hydrogen bromide in acetic acid (6 ml.). After 2 min. the optical rotation $[\alpha]_D$ had decreased from +157° (in acetic acid) to +137° and after 16 min. had reached +88°, then remaining constant. An excess of water was then added and the solid (0·87 g.) collected, washed with water, and dried. Crystallisation from benzene–*n*-hexane and finally ethyl acetate–*n*-hexane gave colourless rods of the 2 : 4-dibromo-ketone (VIII; R = H), m. p. 172—173° (decomp.), $[\alpha]_D^{23}$ +87°. Recrystallisation from the same solvent mixture gave a product, m. p. 174—176° (decomp.), $[\alpha]_D^{23}$ +85°, $[\alpha]_D^{21}$ +69° (acetone), $\lambda_{max.}$ 210 and 292 mμ (ε 2580 and 141 respectively), $\nu_{max.}$ 1746 and 1230 (21-OAc), 1725 (20-CO), and 1708 cm.$^{-1}$ (CO) (Found: C, 49·2; H, 5·3; Br, 27·9. Calc. for $C_{23}H_{30}O_6Br_2$: C, 49·1; H, 5·4; Br, 28·4%). [Rosenkranz *et al.*[5] give m. p. 150—153° (decomp.).] A 49% yield of the 2 : 4-dibromo-ketone was obtained by starting with a suspension of the 2 : 2-dibromo-compound (3·4 g.) in acetic acid (100 ml.) containing hydrogen bromide.

21-*Acetoxy*-2 : 4-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = H) *from* 4 : 5α-*Dihydrocortisone Acetate* (V; R = H).—Bromine (24·9 g., 2·1 mol.) in acetic acid (100 ml.) was added during 4 min. to a rapidly stirred fine suspension (60-mesh sieve) of 4 : 5-dihydrocortisone acetate (V; R = H) (30 g.) in acetic acid (350 ml.) at 16°, containing hydrogen bromide (22 ml.; 6·8N-solution in acetic acid; 2 mol.). The cooling-bath was removed and the solution stirred for a further 10 min., poured into water, and extracted with methylene chloride. The extract was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated under reduced pressure to small bulk. Ethyl acetate (100 ml.) was added and the solution evaporated *in vacuo*. The solid residue (41 g.) containing solvent (9 g.) was added with stirring to a boiling mixture of pure ethyl acetate (17·5 ml.) and *cyclo*hexane (22·5 ml.), whereupon the 2 : 4-dibromo-ketone (VIII; R = H) separated. The slurry was cooled to room temperature and diluted with benzene (50 ml.) and the solid collected, washed with benzene, then *n*-hexane, and air-dried {28·1 g., 68%; m. p. 173—175° (decomp.); $[\alpha]_D^{20}$ +85° (Found: Br, 27·3%)}.

Dehalogenation of the residue from the evaporated filtrate (12·5 g.) with sodium iodide and oxalic acid as described for the reduction of (XI), and crystallisation of the product twice from acetone furnished 4 : 5α-dihydrocortisone acetate (V; R = H) (2·9 g.), m. p. 230—233°, $[\alpha]_D^{20}$ +102°, identical with an authentic specimen.

When the acetate (V; R = H) was dibrominated in solution in acetic acid, the product was isolated after 15 hr. at room temperature. Chromatography on alumina gave, on elution with benzene–light petroleum, 17α : 21-diacetoxy-2-bromo-5α-pregnane-3 : 11 : 20-trione (VI; R = Ac), as prisms (from methanol) (12%), m. p. 220—223°, $[\alpha]_D^{20}$ +42°, identified with an authentic specimen by its infrared spectrum (see below). Benzene eluted the 2 : 4-dibromo-ketone (VIII; R = H; 20%), m. p. 170—172° (decomp.), $[\alpha]_D^{20}$ +86°.

Reaction of 21-*Acetoxy*-2 : 4-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = H) *with Sodium Iodide*.—(a) *Preliminary investigations*. Crystalline trione (1 g.) in acetone (200 ml.) containing sodium iodide (2·12 g., 4 mol.) was refluxed under nitrogen. Samples (10 ml.) of the mixture were removed at intervals, the free iodine being estimated by titration with 0·1N-sodium thiosulphate and the intensity of absorption at 239 mμ recorded. Both values reached a steadily but slowly increasing value after 4 hr. (*ca.* 1·25 mol. of iodine; $E^{1\%}_{1\ cm.}$ 135). In more concentrated solution, *e.g.*, steroid (1 g.) in acetone (50 ml.) containing sodium iodide (4 g.), similar figures were reached in 1—1½ hr. The iodine content of the steroid was 18—20% (Calc. for $C_{23}H_{29}O_6I$: I, 24·0%) at this stage but fell steadily, with subsequent increase in intensity of light absorption and amount of free iodine as the time of reflux was prolonged. After 24 hr. the iodine content of the steroid had fallen to 15% in the dilute, and 8% in the more concentrated, conditions. The precipitation of sodium bromide (0·365 g.) from mixtures containing the 2 : 4-dibromo-ketone (1 g.) was in accordance with complete replacement or elimination by iodine (2 mol., 0·366 g.), coinciding approximately with the termination of the initial rapid increase in light absorption.

(b) *Crude* 2-*iodocortisone acetate* (XI; R = H) *and crude cortisone* 21-*acetate* (XII; R = H). The 2 : 4-dibromo-compound (20 g.) was treated as described for the concentrated conditions

in (a). After 2½ hours' refluxing the iodine was removed with 0·1N-sodium thiosulphate. Water was then added and the product extracted with methylene chloride, yielding 2-iodocortisone acetate (18·2 g.), $\lambda_{max.}$ 240 ($E^{1\%}_{1\,cm.}$ 205) (Found: I, 21·5. Calc. for $C_{23}H_{29}O_6I$: I, 24·0%). A sample reprecipitated from water–methanol showed $\lambda_{max.}$ 241 mμ ($E^{1\%}_{1\,cm.}$ 235) (Found: I, 21·0%), m. p. 139—140°, $[\alpha]_D^{20}$ +199°, +170° (in acetone). The substance readily decomposed in chloroform solution, the colour of free iodine appearing. The crude iodo-compound was treated in acetone (300 ml.) with 1·2N-chromous chloride (200 ml.) under carbon dioxide. After 30 min., the solution was diluted with water and extracted with ethyl acetate. The extract was washed and evaporated, to yield crude cortisone acetate (XII; R = H) (14·2 g.), m. p. 215—218°, $[\alpha]_D^{20}$ +188°, $\lambda_{max.}$ 238 mμ ($E^{1\%}_{1\,cm.}$ 268).

(c) *Crude cortisone* 21-*acetate* (XII; R = H): *general methods.* Bromine (26·78 ml.) was added to acetone (750 ml.) with cooling and, when this solution became colourless, sodium carbonate (70 g.) was added with stirring and continued cooling. When free from hydrogen bromide (20—30 min.), the solution was filtered and the filtrate added to hot acetone (2·7 l.) containing sodium iodide (700 g.). This solution was refluxed for 15 min., whereafter the crude 2:4-dibromo-ketone (VIII; R = H) (139 g.) from 4:5α-dihydrocortisone acetate (160 g.) was added. Refluxing was continued for 2½ hr. during which much free iodine appeared. Oxalic acid (139 g.; commercial) was then added and the mixture refluxed for a further hour; then it was cooled, ethyl acetate (3 l.) added, and the solid filtered off. The filtrate was washed with water, sodium hydrogen carbonate solution, and water, and the remaining free iodine removed with zinc dust (350 g.) and acetic acid (30 ml.). The mixture was filtered, and the filtrate washed with water, then sodium hydrogen carbonate solution, and evaporated to dryness, giving crude cortisone acetate (XII; R = H) (97 g.), $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 265), m.p. 209—215°, $[\alpha]_D^{20}$ +188°.

Isolation of Cortisone 21-*Acetate* (XII; R = H) *from a Crude Mixture by Means of Girard* P *Reagent.*—A crude mixture containing cortisone acetate ($\lambda_{max.}$ 238 mμ, $E^{1\%}_{1\,cm.}$ 271), $[\alpha]_D$ +182° (13·4 g.), Girard P reagent (6·7 g.), anhydrous ethanol (200 ml.), and glacial acetic acid (10 ml.) was refluxed for 30 min. The solution was cooled to 20°, 40% aqueous formaldehyde solution (27 ml.) added, and the whole kept at room temperature for 25 min., then poured into 4% aqueous sodium hydrogen carbonate (500 ml.) and extracted with ethyl acetate (3 × 150 ml.). The extracts were combined, washed with water, dried, and evaporated under reduced pressure to give crude dihydrocortisone acetate (V; R = H) (4·53 g.), $\lambda_{max.}$ 238 mμ ($E^{1\%}_{1\,cm.}$ 90), $\nu_{max.}$ 1742 and 1232 (OAc), 1728 (20-CO), 1705 (CO), weak 1658, 1616, and 1600 cm.$^{-1}$ (αβ-unsaturated ketone) (fraction *A*, see below). The aqueous layer after extraction was acidified to pH 1 with hydrochloric acid and set aside for 2 hr. The resulting precipitate was filtered off, washed and dried [7·22 g.; $\lambda_{max.}$ 237·5 mμ (ε 14,800)]. After treatment with charcoal, recrystallisation from ethyl acetate gave cortisone acetate (XII; R = H) as plates, m. p. 243—244°, $[\alpha]_D^{20}$ +220°, $\lambda_{max.}$ 237·5 mμ (ε 15,500), $\nu_{max.}$ 1745 and 1230 (21-OAc), 1726 (20-CO), 1705 (CO), 1662, 1618, and 864 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 68·8; H, 7·6 Calc. for $C_{23}H_{30}O_6$: C, 68·6; H, 7·5%).

The filtrate from the cortisone acetate precipitation was extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated under reduced pressure, to give a pale yellow solid (1·483 g.), $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 332), $\nu_{max.}$ weak 1742 and 1232 (21-OAc), 1728 (20-CO), 1708 (CO), 1662, 1616, and 1600 cm.$^{-1}$ (αβ-unsaturated ketone), $[\alpha]_D$ +183°. Reacetylation in pyridine–acetic anhydride, Girard P separation, and crystallisation yielded cortisone 21-acetate (1 g.), $\lambda_{max.}$ 238 mμ (ε 15,000), identified as above. The material from the mother-liquors from this crystallisation, on chromatography on acid-washed alumina in ether–chloroform, gave a large fraction (40%) showing $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 364—398) and a greatly enhanced conjugated ketone band at 1662 cm.$^{-1}$, considerably more intense than that of cortisone acetate itself. This compound is tentatively formulated as 21-acetoxy-17α-hydroxypregna-4:8(9)-diene-3:11:20-trione originating from a 9-bromo-ketone.[13]

Fraction *A* (see above), on crystallisation, hydrogenation over palladium–charcoal, and recrystallisation from ethyl acetate, gave 4:5α-dihydrocortisone 21-acetate in 50% yield from the crude material. A filtrate from the crystallisation before hydrogenation was evaporated to dryness and triturated with ether–benzene, and the insoluble crystalline residue was filtered off and identified as 21-acetoxy-3β:17α-dihydroxy-5α-pregnane-11:20-dione (Reichstein's D monoacetate), m. p. 237—238°, $[\alpha]_D^{20}$ +89°, +66° (in acetone), $\nu_{max.}$ (in Nujol) 3530 and 3450 (OH), 1752 and 1231 (21-OAc), 1730 (20-CO) and 1695 cm.$^{-1}$ (CO). Pataki *et al.*[28] give m. p. 235—237°, $[\alpha]_D^{20}$ +66° (in acetone).

3β : 17α : 21-*Triacetoxy-5α-pregn-2-ene*-11 : 20-*dione* (XIII).—(*a*) 60% Aqueous perchloric acid (0·125 ml.) was added to acetic anhydride (100 ml.) at 0°. The resulting solution was shaken with a suspension of 21-acetoxy-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (50 g.) in benzene (800 ml.) at room temperature for 20 min. The whole was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated, to yield a solid that was washed with a little ether and crystallised from methanol. The *triacetate* (XIII) (45 g.) separated as needles, m. p. 175—181°, $[\alpha]_D$ +46°, $\nu_{max.}$ (in CS_2) 1752 and 1218 (enol OAc), 1740 and 1236 (OAc), and 1710 cm.$^{-1}$ (CO) (Found: C, 66·4; H, 7·5. $C_{27}H_{36}O_8$ requires C, 66·4; H, 7·4%).

(*b*) (Cf. Huang-Minlon *et al.*[15b]) 21-Acetoxy-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (3 g.) was stirred with toluene-*p*-sulphonic acid (1·75 g.) and acetic anhydride (38 ml.) for 17 hr. The product was cooled to 0° and water (150 ml.) added. After the mixture had been stirred at 0° for 1 hr. and room temperature for 2½ hr., the solid was collected and twice crystallised from methanol, to yield the triacetate (1·77 g.), m. p. 175—181°, $[\alpha]_D$ +46°, identical with the specimen described above.

17α : 21-*Diacetoxy-2-bromo-5α-pregnane*-3 : 11 : 20-*trione* (VI; R = Ac).—(*a*) A 1·32N-solution of bromine in acetic acid (76 ml., 1·0 mol.) was added in one portion to a solution of the triacetate (XIII) (24 g.) in acetic acid (100 ml.) at room temperature. The colour disappeared almost immediately and the product crystallised. After a further 15 min., the solid (18 g.) was collected, washed with ether, dried, and recrystallised from acetone, to give the 2-*bromo-ketone* (VI; R = Ac) as colourless rhombs, m. p. 230—232° (decomp.), $[\alpha]_D$ +45°, $\nu_{max.}$ 1735 and 1232 (OAc), and 1710 cm.$^{-1}$ (CO) (Found: C, 57·3; H, 6·3; Br, 15·5. $C_{25}H_{33}O_7Br$ requires C, 57·2; H, 6·3; Br, 15·2%).

(*b*) *Bromination of* 17α : 21-*diacetoxy-5α-pregnane*-3 : 11 : 20-*trione* (V; R = Ac). The diacetate (V; R = Ac) (described below) was brominated in the same way as the triacetate (XIII), yielding 80% of the same 2-bromo-ketone (VI; R = Ac), m. p. 230—232° (decomp.), $[\alpha]_D$ +45°.

17α : 21-*Diacetoxy-5α-pregnane*-3 : 11 : 20-*trione* (VI; R = Ac).—(*a*) The 2-bromo-ketone (VI; R = Ac) (4 g.) was dehalogenated in acetone by excess of chromous chloride solution. Crystallisation of the product from acetone gave needles of the *diacetate* (V; R = Ac) (2·8 g.), m. p. 228—230°, $[\alpha]_D$ +32°, $\nu_{max.}$ 1732 and 1232 (OAc), and 1700 cm.$^{-1}$ (CO) (Found: C, 67·3; H, 7·7. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·7%).

(*b*) Concentrated hydrochloric acid (24 ml.) was added to a solution of the triacetate (XIII) (10 g.) in a mixture of chloroform (100 ml.), methanol (350 ml.), and water (35 ml.). After 20 hr. at room temperature, water was added, and the chloroform layer separated, washed with aqueous sodium hydrogen carbonate, then with water, and dried ($MgSO_4$). Evaporation gave a gum which was acetylated with acetic anhydride (60 ml.) and pyridine (100 ml.) at room temperature, and the diacetate (V; R = Ac) was crystallised from acetone. It (7 g.), had m. p. 228—230°, $[\alpha]_D$ +32°.

Alkaline Hydrolysis of the Triacetate (XIII) *and the Diacetate* (V; R = Ac).—The triacetate (1 g.) in methanol (100 ml.) was treated with aqueous 0·1N-sodium hydroxide (41 ml., 2 mol.) under nitrogen for 5 min. Water was added and the mixture extracted with methylene chloride. Evaporation of the solvent gave a product which, after acetylation with acetic anhydride (6 ml.) and pyridine (10 ml.) at room temperature, crystallised from ethyl acetate to give 21-acetoxy-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (V; R = H) (0·5 g.), m. p. 230°, $[\alpha]_D$ +100°. A similar product was obtained by use of 3 equivs. of alkali. The diacetate treated with one or two equivs. of alkali yielded the same product (V; R = H).

17α : 21-*Diacetoxy*-2 : 2-*dibromo-5α-pregnane*-3 : 11 : 20-*trione* (VII; R = Ac).—Bromine in acetic acid (1·15N; 24 ml., 1·3 mol.) was added in one portion to a solution of 17α : 21-diacetoxy-2-bromo-5α-pregnane-3 : 11 : 20-trione (VI; R = Ac) (5 g.) in acetic acid (750 ml.) containing potassium acetate (7·5 g.) and acetic anhydride (0·75 ml.). The solution was maintained at 85° for 1½ hr., by which time all the bromine had reacted. Water (4 l.) was added to the cooled solution; the precipitated solid, when dried and crystallised from methylene chloride–ether, yielded the 2 : 2-*dibromo-ketone* (VII; R = Ac) (3·79 g.), m. p. 153—155°, resolidified and melted 195—215° (decomp.), $[\alpha]_D$ +77° (Found: C, 49·7; H, 5·2; Br, 25·6. $C_{25}H_{32}O_7Br_2$ requires C, 49·7; H, 5·3; Br, 26·45%).

17α : 21-*Diacetoxy*-2 : 4-*dibromo-5α-pregnane*-3 : 11 : 20-*trione* (VIII; R = Ac).—(*a*) A solution of the 2 : 2-dibromo-ketone (VII; R = Ac) (2 g.) in dry alcohol-free chloroform (101 ml.) containing hydrogen bromide (1·37 g.) was set aside for 3 hours. The mixture was then washed with sodium hydrogen carbonate solution, and water, and the solvent removed under

reduced pressure to give the 2 : 4-*dibromo-ketone* (VIII; R = Ac) (1·99 g.), m. p. 185° (decomp.), $[\alpha]_D^{20}$ +26°, $\nu_{max.}$ 1732 and 1236 (OAc), and 1710 cm.$^{-1}$ (CO) (Found: C, 49·4; H, 5·1; Br, 25·8%).

(*b*) Bromine in dry alcohol-free chloroform (0·504N; 161 ml.) was added rapidly to a solution of the above triacetate (XIII) (20 g.) in chloroform containing hydrogen bromide (13·6 g.). Then more bromine in chloroform (0·504N; 161 ml.) was added during 0·5 hr. The solution was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated *in vacuo* at room temperature. Trituration of the residue with ether and the removal of the solvent *in vacuo* gave the 2 : 4-dibromo-compound (VIII; R = Ac), m. p. 180° (decomp.), $[\alpha]_D$ +27°, quantitatively.

17α : 21-*Diacetoxypregn*-4-*ene*-3 : 11 : 20-*trione* (*Cortisone Diacetate*) (XII; R = Ac).—Bromine (3·4 ml.) was added to acetone (250 ml.), and when the solution became colourless, sodium carbonate (10 g.) was added. The mixture was occasionally shaken for 30 min. and then filtered into sodium iodide (100 g.) in acetone (300 ml.). After the solution had been refluxed for 0·5 hr., the 2 : 4-dibromo-compound (VIII; R = Ac) (20 g.; crude from the previous experiment) was added and the mixture refluxed for 4½ hr. Oxalic acid (20 g.) was added and the mixture refluxed for a further ½ hr., diluted with ethyl acetate (1 l.), and filtered, and the organic layer in the filtrate was washed with water, saturated aqueous sodium hydrogen carbonate, and water. Acetic acid (5 ml.) and zinc dust (25 g.) were added and the solution was shaken until colourless. The zinc was filtered off and the filtrate washed with water, saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation gave a yellow solid (13·1 g.), $\lambda_{max.}$ 237·5 mμ ($E_{1\,cm.}^{1\%}$ 250). This product was refluxed with Girard reagent P (13·1 g.) and ethanol (300 ml.) containing acetic acid (30 ml.) for 0·5 hr., the solution cooled to room temperature, and 40% aqueous formaldehyde (50 ml.) added. After 0·5 hr. the mixture was poured into saturated aqueous sodium hydrogen carbonate (1560 ml.) and extracted with ethyl acetate (3 × 300 ml.). The solvent was evaporated from the combined ethyl acetate layers to yield a solid (5·2 g.), $\lambda_{max.}$ 246 mμ ($E_{1\,cm.}^{1\%}$ 70). The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid, and after 3 hr. was extracted with ethyl acetate (2 × 250 ml.). The extract was washed as previously and evaporated, to yield a solid (7 g.), m. p. 207—214°, $\lambda_{max.}$ 238 mμ ($E_{1\,cm.}^{1\%}$ 345). Crystallisation from methanol gave cortisone diacetate (XII; R = Ac) (5·3 g.) as colourless thick needles, m. p. 218—220°, $[\alpha]_D$ +128°, $\lambda_{max.}$ 238 mμ (ε 15,300), $\nu_{max.}$ 1735 and 1230 (OAc), 1707 (CO), 1664, 1616, and 864 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 67·7; H, 7·2. Calc. for $C_{25}H_{32}O_7$: C, 67·55; H, 7·3%). Huang-Minlon *et al.*[15b] give m. p. 221—222°, $[\alpha]_D^{23}$ +133°, $\lambda_{max.}$ 238 mμ (log ε 4·2 in MeOH). Moffett and Anderson[28] give m. p. 216·5—218°.

Conversion of Cortisone Diacetate (XII; R = Ac) *into Cortisone Acetate* (XII; R = H).—A N-solution of sodium ethoxide in methanol (14 ml.) was added to cortisone diacetate (XII; R = Ac) (9·47 g.) in methanol (500 ml.). After 5 min. at room temperature, a few ml. of water were added and the alkali was neutralised with acetic acid. The mixture was concentrated *in vacuo*, diluted with water, and extracted with methylene chloride. The extract was washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue acetylated with pyridine (50 ml.) and acetic anhydride (30 ml.) at room temperature for 1 hr. Working up in the usual way gave crude cortisone acetate (XII; R = H) (7·5 g.), $[\alpha]_D$ +224°, m. p. 210—230°, $\lambda_{max.}$ 238 mμ ($E_{1\,cm.}^{1\%}$ 365). Crystallisation from methanol gave the pure compound, m. p. 236—240°, $[\alpha]_D$ +220°, $\lambda_{max.}$ 238 mμ (ε 14,900), identified with authentic material by its infrared spectrum.

4α-*Bromocholestan*-3-*one* (XV*a*).—A solution of 2 : 4-dibromocholestan-3-one (20 g.) in anhydrous alcohol-free chloroform (175 ml.) and acetic acid (370 ml.) was treated with 93% chromous acetate (20 g., 2·3 mol.). Vigorous stirring and an atmosphere of nitrogen were maintained throughout the experiment. After 30 min. water was added and the product (16·7 g.), $[\alpha]_D^{21}$ +13°, isolated by chloroform. Several crystallisations from methyl acetate gave 4α-*bromocholestan*-3-*one* (XV*a*) as rods (3·63 g.), m. p. 144—146°, $[\alpha]_D^{24}$ ±0°, $\lambda_{max.}$ 283 mμ (ε 25), $\nu_{max.}$ (in CS_2) 1730 cm.$^{-1}$ [minor peaks at 1168, 828, and 730 cm.$^{-1}$ distinguish the spectrum from that of the 2-bromo-isomer (XIV)] (Found: C, 69·3; H, 9·75; Br, 16·45. $C_{27}H_{45}OBr$ requires C, 69·6; H, 9·7; Br, 17·2%).

Cholest-4-*en*-3-*one*.—Powdered semicarbazide (322 mg., 2 mol.) was added to 4-bromocholestan-3-one (XV*a*) (1·0 g.) in alcohol-free chloroform (17 ml.) and *tert.*-butanol (30 ml.), and the mixture shaken under nitrogen for 30 min. The orange-yellow colour reached maximum intensity in 13 min., and then faded. The solvents were evaporated under reduced pressure

[28] Moffett and Anderson, *J. Amer. Chem. Soc.*, 1954, **76**, 747.

and the residue was triturated with ethanol (15 ml.) and water (10 ml.), and the solid filtered off and dried (0·9 g.). Crystallisation from ethanol–ethyl acetate gave 3-semicarbazonocholest-4-ene (0·63 g., 66%), m. p. 235—237° (decomp.), $[\alpha]_D^{25}$ +133°, $\lambda_{max.}$ 270 mμ (ε 26,400 in EtOH). The semicarbazone (0·59 g.) was decomposed according to Hershberg's method, giving cholest-4-en-3-one (0·27 g., 55%), m. p. 77—79°, $[\alpha]_D^{23}$ +87°, $\lambda_{max.}$ 242·5 mμ (ε 15,000), identity being confirmed by the infrared spectrum.

2α : 4α-*Dibromocholestan-3-one from* 4-*Bromocholestan-3-one* (XV*a*).—The 4-bromo-ketone (0·8 g.) in acetic acid (50 ml.) containing hydrogen bromide (6·8N in acetic acid; 0·25 ml., 1 mol.) was treated with a solution of bromine (0·325 g., 1·1 mol.) in acetic acid (3 ml.). After 10 min. the solution was diluted with water (400 ml.), and the solid collected, washed, and dried (0·95 g.). Recrystallisation from light petroleum (b. p. 60—80°) gave needles of 2α : 4α-dibromocholestan-3-one (0·48 g., 51%), m. p. 192—194°, $[\alpha]_D^{23}$ ±0°, identified by its infrared spectrum (Found: Br, 29·6. Calc. for $C_{27}H_{44}OBr_2$: Br, 29·3%).[19]

21-*Acetoxy*-4-*bromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (XV*b*).—(*a*) 21-Acetoxy-2 : 4-dibromo-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (VIII; R = H) (10 g.) in acetone (50 ml.) and methanol (150 ml.) containing concentrated hydrochloric acid (5 ml.) was treated at −45°, under nitrogen, with 1·4N-chromous chloride (22·25 ml., 1·75 mol.) in 8 min. The mixture was allowed to warm to room temperature, and the product was precipitated with water and filtered off (8·75 g.). Several crystallisations from ethyl acetate gave rods of 21-*acetoxy*-4-*bromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (XV*b*) as the *solvate* (2·21 g., 21%), m. p. 206—208° (decomp.), $[\alpha]_D^{22}$ +47° (*c* 1·26) (Found: C, 57·0; H, 6·9; Br, 14·0. $C_{23}H_{31}O_6Br,C_4H_8O_2$ requires C, 56·7; H, 6·9; Br, 14·0%). The solvent-free compound, obtained from benzene, had m. p. 204—206° (decomp.), $[\alpha]_D^{26}$ +56°, +42° (in acetone), $\lambda_{max.}$ 292 mμ (ε 122), $\nu_{max.}$ 1745 and 1234 (OAc), 1726 (20-CO) and 1708 cm.$^{-1}$ (CO) (Found: C, 57·35; H, 6·5; Br, 16·3. $C_{23}H_{31}O_6Br$ requires C, 57·15; H, 6·5; Br, 16·5%).

(*b*) The 2 : 4-dibromo-compound was prepared in solution in acetic acid from 4 : 5α-dihydrocortisone 21-acetate (40 g.) as described above. The solution from the bromination was used without further treatment. A stream of carbon dioxide was passed through it with stirring for 5 min., then 2·28N-chromous chloride (104·4 ml.) was added during 70 min. through a jet immersed in the liquid. The 4-bromo-compound (XV*b*) was precipitated by water, filtered off, and dried (43 g., 92%; $[\alpha]_D$ +74°) (Found: Br, 15·5%). The best yields of pure product were obtained when the bromine values lay between 15 and 16%. Crystallisation from aqueous acetic acid followed by ethyl acetate gave the 4-bromo-ketone (XV*b*) as the solvate (24·05 g.), $[\alpha]_D$ +51°. Identity with the pure material described above was established by the infrared spectrum.

Cortisone 21-*Acetate* (XII; R = H) *from the* 4-*Bromo-compound* (XV*b*).—The 4-bromo-compound (XV*b*) (23·5 g.; ethyl acetate solvate; prepared as in the last experiment) in *tert.*-butanol (395 ml.) and alcohol-free chloroform (198 ml.) was added to a suspension of finely powdered semicarbazide (7·5 g.) in similar quantities of the two solvents. An atmosphere of carbon dioxide was maintained and the mixture set aside for 1½ hr., being shaken occasionally. The solvents were removed under reduced pressure and the residue was triturated with hot ethanol (535 ml.) to which water (1·5 l.) was then added. The solid was filtered off, washed, and taken up in hot acetic acid (640 ml.). 50—60% Aqueous pyruvic acid (10·6 ml.) in water (200 ml.) was added and the solution kept overnight at room temperature, then warmed to 60° for 30 min. The product, isolated by chloroform, was cortisone 21-acetate (16·15 g., 98%), m. p. 225—227°, $[\alpha]_D$ +213°, $\lambda_{max.}$ 237 mμ (ε 14,400). Crystallisation from acetone gave needles (desolvated at 100—120°/0·2 mm.) (13·64 g., 84·3%), m. p. 238—240°, $[\alpha]_D$ +219°, $\lambda_{max.}$ 237 mμ (ε 14,700).

Cortisone 21-*Acetate from the Crude Mixture of* 2- *and* 4-*Bromo-compounds.*—(a) *Replacement of the* 2-*bromine atom by iodine.* 21-Acetoxy-2-bromo-17α-hydroxypregnane-3 : 11 : 20-trione (1 g.) in acetone (30 ml.) containing sodium iodide (1·3 g.) was refluxed for 7 hr. under nitrogen. Isolation, treatment with dilute sodium thiosulphate solution, and crystallisation from methanol gave the iodo-trione (XVIII*b*) (0·62 g.), m. p. 191° (decomp.), $[\alpha]_D^{20}$ +107°, $\lambda_{max.}$ 252 mμ (ε 1010), giving all the usual infrared bands for the functional groups (Found: I, 20·5. Calc. for $C_{23}H_{31}O_6I,CH_3{\cdot}OH$: I, 22·6%).

(b) *Stability of the* 4-*bromine atom to the above conditions.* The 4-bromo-compound (XV*b*), m. p. 181° (decomp.), $[\alpha]_D$ +61° (Found: Br, 16·3%) (0·3 g.), in acetone (7 ml.) containing

[19] Ruzicka, Bossard, Fischer, and Wirz, *Helv. Chim. Acta*, 1936, **19**, 1151; Butenandt, Schramm, Wolff, and Kudszus, *Ber.*, 1936, **69**, 2779; Inhoffen, *Ber.*, 1937, **70**, 1695; Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1712; Djerassi and Scholz, *ibid.*, 1948, **70**, 417.

sodium iodide (0·3 g.) was refluxed for 1 hr. No sodium bromide separated when the solution was cooled, and the product was precipitated, by the addition of dilute sodium thiosulphate solution, as a white powder (0·30 g.), m. p. 180—181° (decomp.), $[\alpha]_D$ +61°; no appreciable ultraviolet absorption (Found: Br, 14·7%).

(c) *Application of the above conditions to the mixture.* The mixture of the 2- and 4-bromosteroids (3 g.; $[\alpha]_D$ +76°; Br, 17·5%) from the chromous chloride reduction of the 2 : 4-dibromo-compound (VII; R = H), was refluxed with sodium iodide (3 g.) in acetone (60 ml.) for 1 hr. and then the whole was poured into 1% sodium thiosulphate solution. The precipitate was filtered off and treated in acetone (160 ml.) with 0·7N-titanous chloride (30 ml.) for 15 min. Dilution and extraction with chloroform gave an iodine-free product (2·71 g.) (Found: Br, 9·0%). This material (2·61 g.) in chloroform (50 ml.) and *tert.*-butanol (65 ml.) was treated with semicarbazide base (0·7 g.) under carbon dioxide for 15 min. at room temperature. The solvent was removed under reduced pressure and the residue triturated with ethyl alcohol (35 ml.) and water (25 ml.). The solid was filtered off and treated with 1·0N-pyruvic acid (9 ml.) in acetic acid (55 ml.) and water (18 ml.) at 60°. The solution was then kept at room temperature for 18 hr. Dilution with water and extraction gave crude cortisone acetate (1·92 g.), $\lambda_{max.}$ 238 mμ ($E^{1\%}_{1\,cm.}$ 220), which was subjected to the separation by Girard P reagent as already described. The 4 : 5α-dihydrocortisone acetate fraction gave 0·8 g., $\lambda_{max.}$ 239 mμ (ε 920). The cortisone acetate fraction gave 1·0 g., $\lambda_{max.}$ 238 mμ (ε 14,100), which yielded on crystallisation from ethyl acetate 0·835 g., m. p. 240—242°, $[\alpha]_D$ +216°, $\lambda_{max.}$ 237 mμ (ε 14,200), identified by its infrared spectrum.

21-Acetoxy-2 : 4-dibromo-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (VIII; R = H) *from the 4-Bromo-ketone* (XV*b*).—The 4-bromo-compound (XV*b*) (7 g.) in acetic acid (205 ml.) containing hydrogen bromide (6·8N in acetic acid; 21·1 ml., 1 mol.) was treated with bromine (2·435 g., 1·05 mol.) in acetic acid (21 ml.). The product (8·98 g.) was isolated by methylene chloride and after crystallisation from ethyl acetate–*cyclo*hexane (3·5 + 3·5 ml.) yielded the 2 : 4-dibromo-compound (VIII; R = H) (6·48 g., 80%), m. p. 172—176° (decomp.), $[\alpha]_D^{22}$ +76° (Found: C, 48·8; H, 5·5; Br, 28·6%). After being kept in acetone containing lithium bromide for 18 hr. at room temperature this product gave a 2 : 4-dibromo-ketone (VIII; R = H), m. p. 165—173° (decomp.), $[\alpha]_D^{22}$ +83° (Found: C, 49·3; H, 5·5; Br, 28·3%). We attribute the differences between these two bromo-ketones to epimerism about the C–Br bonds.

4-Bromo-2-iodocholestan-3-one (XVI*a*).—4-Bromocholestan-3-one (XV*a*) (0·5 g.) in acetic acid (25 ml.) was treated at 75° with iodine monochloride (0·35 g., 2 mol.) in acetic acid (8 ml.). After 8 min. the product was precipitated with water at 0° and filtered off (0·55 g.). Crystallisation from aqueous acetone gave needles of *4-bromo-2-iodocholestan-3-one* (XVI*a*) (0·32 g., 47%), m. p. 154—158° (decomp.), $[\alpha]_D^{23}$ −8°, $\lambda_{max.}$ 254 mμ (ε 810) (Found: 14·92 mg. gave 9·8 mg. of Ag halide. $C_{27}H_{44}OBrI$ requires 10·3 mg.).

Deiodination. 4-Bromo-2-iodocholestan-3-one (0·3 g.) in ether (10 ml.) and benzene (10 ml.) was shaken for 3 hr. with 10% aqueous sodium hydrogen sulphite solution (25 ml.). Separation and evaporation of the solvents gave a residue which on crystallisation from *n*-hexane gave rods of 4-bromocholestan-3-one (XV*a*) (0·11 g., 47%), m. p. 144—145°, $[\alpha]_D$ +1° (Found: Br, 16·95%). Identification was confirmed by the infrared spectrum.

Sodium iodide (2 g.) in ethyl methyl ketone (25 ml.) was added to 2 : 4-dibromocholestan-3-one (2 g.) in ethyl methyl ketone, and the solution kept at 20° for 30 min. Sodium bromide was precipitated and filtered off (Found: 370 mg. Calc. for 1 mol.: 380 mg.). Sodium thiosulphate solution was added until the free iodine was just removed and the product precipitated with water, yielding a solid (1·85 g.), $[\alpha]_D$ −5°, which crystallised from acetone as plates of bromoiodocholestan-3-ones (XVI*a* and XVII*a*), m. p. 174—176° (decomp.), $[\alpha]_D$ −16° (Found: Ag halide, 4·715 mg. from 6·553 mg. of steroid. Calc. for $C_{27}H_{44}OBrI$: Ag halide, 4·690 mg.).

This bromoiodo-ketone (0·561 g.) was shaken for 3 hr. in ether (10 ml.) and benzene (10 ml.) with 10% aqueous sodium hydrogen sulphite (25 ml.). The product, isolated in the usual manner, crystallised from *n*-hexane as rods (0·111 g.), m. p. 140—142° (decomp.), $[\alpha]_D^{23}$ +26° (Found: Br, 16·7%). The infrared spectrum showed bands due to both 2- and 4-bromocholestan-3-one.

The authors of this and the five preceding papers are indebted to Dr. J. E. Page for interpretation of infrared spectra. Thanks are also offered to Messrs. Brooks, Collins, Green, Halcox, Mooney, Palmer, and Thomas for assistance with the experimental work.

Glaxo Laboratories, Ltd., Greenford, Middlesex. [*Received, May 14th,* 1956.]

839. *Barringtogenol and Barringtogenic Acid, Two New Triterpenoid Sapogenins.*

By R. Anantaraman and K. S. Madhavan Pillai.

Two new triterpenoid sapogenins have been isolated from the fruits of *Barringtonia racemosa* Roxb. The evidence suggested that one, barringtogenol, was 2 : 3 : 23 : 28-tetrahydroxyolean-12-ene (I; R = CH_2·OH) and the other, barringtogenic acid, 2 : 3-dihydroxyolean-12-ene-23 : 28-dioic acid (I; R = CO_2H). Confirmation was obtained by identifying the product of the reduction of arjunolic acid [1] by lithium aluminium hydride with barringtogenol and with the product of similar reduction of barringtogenic acid.

The ripe fruits of the tree *Barringtonia racemosa* Roxb. contain a large quantity of saponins, from which, after hydrolysis, two new triterpenoid sapogenins, barringtogenic acid and barringtogenol have been isolated.

Barringtogenic acid, $C_{30}H_{46}O_6$, m. p. 334°, readily yielded a dimethyl ester, diacetyl and dibenzoyl derivatives, and a dimethyl ester diacetate; this accounts for all the oxygen atoms. The presence of the carboxy group or an equivalent carbonyl function was also apparent from the band at 5·8—6·0 μ in the infrared absorption spectrum. The acid resisted hydrogenation over platinum oxide, but was unsaturated towards tetranitromethane. In reaction with perbenzoic acid, the equivalent of one double bond was consumed. Moreover, the rate of uptake of the per-acid was characteristic of members of the β-amyrin group possessing a hindered double bond; barringtogenic acid also failed to react with osmium tetroxide. These facts and the small molecular-rotation difference between the acid and its dimethyl ester (−27 units) [2] point to barringtogenic acid's being a member of the β-amyrin group.

Barton and Jones [2] have shown that, with those members of the α- and the β-amyrin series which possess a $C_{(23)}$- or $C_{(24)}$-carboxyl group, large decreases in molecular-rotation differences are observed between the acid and the 3-acetyl, 3-benzoyl, and 3-oxo-derivatives. Barringtogenic acid and its derivatives show this behaviour (cf. Table) and it can therefore

	$10^{-2}M[\alpha]$						
	Alcohol	Acetate 1	Benzoate 2	Ketone 3	$10^{-2}\Delta_1$	$10^{-2}\Delta_2$	$10^{-2}\Delta_3$
Barringtogenic acid	+361°	+264°	+142°	—	− 97°	−219°	—
Dimethyl barringtogenate	+334°	+199°	—	+202°	−135°	—	−132°

be reasonably concluded that one of the carboxyl groups is at $C_{(23)}$ or $C_{(24)}$. The position of the double bond with respect to the second carboxyl group was deduced from the ready formation of a bromo-lactone. Easy lactonisation is characteristic of carboxylic acids of the β-amyrin series having a double bond γδ to the carboxyl group,[3] and it was accordingly inferred that barringtogenic acid is unsaturated at the 12 : 13-position as in oleanolic acid and also that the second carboxyl group is at $C_{(28)}$. Confirmatory evidence was secured as barringtogenic acid readily yielded a lactone triacetate under conditions devised by Winterstein and Wiegand.[4]

The position of the other hydroxyl group was indicated by the quantitative oxidation of the acid with lead tetra-acetate, the disappearance of 1 mol. of the reagent establishing the existence of an αβ-diol. Further evidence that the two hydroxyl groups are secondary came from chromic acid oxidation of barringtogenic acid; although the product was non-crystalline, it could be converted into a crystalline dimethyl dioxo-ester which was characterised as the dioxime.

[1] King, King, and Ross, *J.*, 1954, 3995.
[2] Barton and Jones, *J.*, 1944, 659.
[3] See *e.g.*, Jeger, *Fortschr. Chem. Org. Naturstoffe*, 1950, **7**.
[4] Winterstein and Wiegand, *Z. physiol. Chem.*, 1931, **199**, 46.

Since further development of the structure depends on the reactions of its companion triterpene barringtogenol these will be considered now.

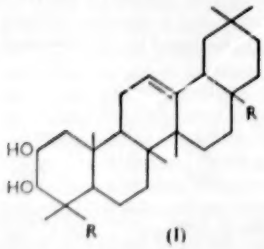
Barringtogenol, $C_{30}H_{50}O_4$, readily yielded tetra-acetyl and tetrabenzoyl derivatives, which could not be hydrolysed with alcoholic potash under ordinary conditions. The triterpene gave a yellow colour with tetranitromethane but resisted hydrogenation with Adams's catalyst. That it contained one double bond was evident from its oxidation with perbenzoic acid.

The molecular-rotation difference between barringtogenol and its tetra-acetate (+12 units) was characteristic for the β-amyrin group of triterpenes, but that between it and the tetrabenzoate (+4 units) was anomalous. Reaction of barringtogenol tetra-acetate with selenium dioxide also suggested that the triterpene belonged to the β-amyrin group, the crystalline diene tetra-acetate having characteristic ultraviolet absorption ($\lambda_{max.}$ 250 and 162 mμ).[5,6]

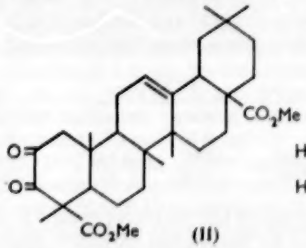
Like barringtogenic acid, barringtogenol is considered to contain an αβ-diol group, from its reaction with periodic acid and with lead tetra-acetate and by formation of an *iso*propylidene derivative. That this group is a 3 : 23-diol was shown by heating barringtogenol with a copper catalyst at 270—290°, small but consistent amounts of formaldehyde being obtained. This behaviour is generally considered typical of the 3 : 23-diol system in triterpenes.[1,7]

The nature of the hydroxyl groups was shown by chromic acid oxidation of barringtogenol. Although the acidic product obtained did not crystallise, it gave a crystalline dimethyl ester which formed a dioxime. Thus, of the four hydroxyl groups two are primary and two secondary.

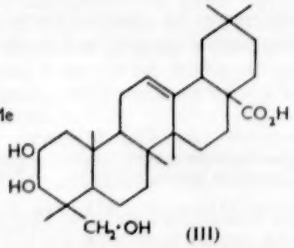
The available evidence therefore indicated a close structural relation between barringtogenol and barringtogenic acid and so an attempt was made to interconvert the two compounds. Dimethyl barringtogenate (I; R = CO_2Me) was reduced with lithium aluminium hydride giving barringtogenol (analysis, etc., and mixed m. p.s of the product and its tetra-acetate). Further, the dimethyl esters (II) obtained by methylation of the acidic products of the oxidation of the two genins with chromic acid were identical.



(I)



(II)



(III)

It is concluded, therefore, that barringtogenol and barringtogenic acid have the structures 2 : 3 : 23 : 28-tetrahydroxyolean-12-ene (I; R = CH_2·OH) and 2 : 3-dihydroxyolean-12-ene-23 : 28-dioic acid (I; R = CO_2H). If these structures are correct, then it is apparent that arjunolic acid,[1] 2 : 3 : 23-trihydroxyolean-12-en-28-oic acid (III), should give a lithium aluminium hydride reduction product identical with barringtogenol and with the lithium aluminium hydride reduction product of dimethyl barringtogenate. Professor F. E. King, F.R.S., kindly provided a sample of the reduction product of arjunolic acid, and this gave no depression in m. p. on admixture with either barringtogenol or with the lithium aluminium hydride reduction product of dimethyl barringtogenate.

Experimental

Rotations were measured in a 2-dm. tube at room temperature, and ultraviolet absorption measurements with a Uvispek spectrophotometer. For analysis, samples were dried at 110°

[5] Ruzicka and Jeger, *Helv. Chim. Acta*, 1942, **25**, 775.
[6] Barton and Holness, *J.*, 1952, 78.
[7] Tsuda and Kitagawa, *Ber.*, 1938, **71**, 1604.

for 2 hr. in a vacuum unless otherwise stated. For chromatography, Merck's alumina, standardised according to Brockmann, was used. Light petroleum signifies material of b. p. 60—80°.

Isolation and Hydrolysis of the Saponins.—Dried ripe fruits were coarsely powdered (after removal of the husk and testa) (4·5 kg.) and extracted successively with 95% and 70% ethanol. The combined extract was evaporated and the residue dissolved in 90% ethanol and reprecipitated by the addition of an equal volume of ether. By repeating the dissolution and precipitation twice, a fairly pure product was obtained, which was completely soluble in water. The solution effected a 100% mortality of fish (*Lebistis reticulata*) in 12 min. (1 in 6000). The purified saponins (600 g.) and 50% ethanol containing 7% sulphuric acid were refluxed for 36 hr. The yield of sapogenin was 195 g.

Isolation of Barringtogenic Acid.—The sapogenin mixture (50 g. lots) was extracted (Soxhlet) successively with carbon tetrachloride and carbon tetrachloride–benzene (1 : 1) for 60 hr. each. The first extract gave a brown (14 g.) and the second a dark brown powder (15·5 g.). These were separately treated (3 times) with 10% aqueous sodium carbonate (500 c.c.) on a water-bath for ½ hr., and filtered. The combined filtrate from each fraction was acidified with dilute hydrochloric acid. From the first extract, only a trace of the acid genin was obtained, while the second gave 12 g. This was readily soluble in ethanol, methanol, and dioxan, but the solutions could not be decolorised without serious loss of material. However, when an alcoholic solution was diluted to turbidity with water and the alcohol partially removed, a precipitate was formed which was appreciably paler. By repeating these operations, a nearly colourless product was obtained, which, after recrystallisation from methanol, gave thick prisms of *barringtogenic acid* (2 g.), m. p. 332—334° (decomp.), $[\alpha]_D$ +72° (*c*, 1·12 in MeOH). The pure genin crystallised from pyridine as small needles. A further 1 g. of the pure material was obtained by chromatography of the residues from the mother-liquors in methanolic solution on purified activated animal charcoal. 12·5 g. of the barringtogenic acid were obtained from 195 g. of crude sapogenin mixture.

Isolation of Barringtogenol.—The residues from the solvent extractions of the mixture of sapogenins were combined after removal of the acid genin, well washed, and dried (yield, 65 g.). The yellowish-brown powder (16 g.) was refluxed with 80% ethanol (300 c.c.) for 4 hr. On cooling, the non-acid genin separated as a gel. This was filtered off and again refluxed with 80% ethanol. The white amorphous powder (10·6 g.) was chromatographed in benzene solution (250 c.c.) on alumina (300 g.); on elution with light petroleum and light petroleum–benzene, *barringtogenol* was obtained. After two crystallisations from acetone and drying in a vacuum this formed needles (5·3 g.), m. p. 290—291°, $[\alpha]_D$ +18° (*c*, 1·22 in pyridine). In all 23 g. of barringtogenol were obtained from the sapogen mixture.

Barringtogenic Acid.—The acid [Found, on sample dried at 180°: C, 71·4, 71·6; H, 9·4, 9·3%; *M* (2 carboxyl groups being assumed), 500, 506 (by titration with alkali); 502, 502 (by analysis of the silver salt). $C_{30}H_{46}O_6$ requires C, 71·7; H, 9·2%; *M*, 502] showed the usual solubility of a triterpene acid. Its solution in sulphuric acid was yellow, becoming orange-brown on storage; Salkowsky reaction, acid layer reddish green; Liebermann–Burchardt reaction, pink, immediately becoming red-brown. Addition of tetranitromethane to a solution of the acid caused yellow coloration. The number of double bonds was estimated by reaction of the acid with perbenzoic acid. The equivalent of 1 double bond was consumed in 120 hr., and the reaction then ceased.

The *diacetate*, prepared by using acetic anhydride and pyridine, formed needles (85%) (from acetone), m. p. 334—336° (decomp.), $[\alpha]_D$ +45° (*c*, 0·86 in MeOH) [Found, on sample dried at 180°: C, 69·8, 69·8; H, 8·4, 8·3%; *M*, 584 (by titration with alkali). $C_{34}H_{50}O_8$ requires C, 69·6; H, 8·6%; *M*, 586]. The *dibenzoate*, obtained from the acid with pyridine and benzoyl chloride, was crystallised successively from acetone–methanol and pyridine, giving clusters of needles (yield, 70%), m. p. 343—344°, $[\alpha]_D$ +20° (*c*, 1·53 in MeOH) [Found, on sample dried at 180°: C, 74·6, 74·5; H, 7·5, 7·5%; *M*, 713 (by titration). $C_{44}H_{54}O_8$ requires C, 74·3; H, 7·7%; *M*, 710]. *Dimethyl barringtogenate* was obtained as silky needles, m. p. 253—254°, $[\alpha]_D$ +63° (*c*, 1·12 in MeOH) (Found, on sample dried at 150°: C, 72·0, 72·2; H, 9·5, 9·5. $C_{32}H_{50}O_6$ requires C, 72·4; H, 9·5%), by treatment of the acid with ethereal diazomethane or dimethyl sulphate. It was not hydrolysed by boiling 10% ethanolic potassium hydroxide during 4 hr. The *ester diacetate*, prepared in the usual way was crystallised from ethanol, and then from acetone–methanol, and formed thick, stout needles (yield, 80%), m. p. 239—240°, $[\alpha]_D$ +32° (*c*, 0·69 in MeOH) (Found, for sample dried at 150°: C, 70·7, 70·5; H, 8·6, 8·6. $C_{36}H_{54}O_8$ requires C, 70·3; H, 8·85%).

Dimethyl didehydrobarringtogenate. To a cold solution of barringtogenic acid (2·3 g.) in glacial acetic acid (40 c.c.) was added dropwise a solution of chromic anhydride (1·5 g.) in acetic acid–water (15 c.c.); the mixture was then set aside at room temperature for 20 hr. The excess of chromic acid was destroyed by the addition of a little methanol and the product extracted with aqueous sodium carbonate. The extract was filtered and then acidified. Since the product could not be crystallised it was esterified; the *ester* (1 g.) formed fine needles (from ethyl acetate), m. p. 218—220°, $[\alpha]_D$ +38° (*c*, 0·81 in MeOH) (Found: C, 73·1; H, 8·9. $C_{33}H_{46}O_6$ requires C, 72·95; H, 8·8%). Its *dioxime* was prepared by refluxing the ester (300 mg.) and hydroxylamine hydrochloride (500 mg.) in pyridine–methanol for 6 hr. The slender needles (from acetone) (200 mg.) had m. p. 288—290°, $[\alpha]_D$ +46° (*c*, 1·02 in MeOH) (Found: C, 69·3; H, 8·7; N, 5·0. $C_{33}H_{48}O_6N_2$ requires C, 69·0; H, 8·8; N, 5·0%).

Lactones.—(*a*) Barringtogenic acid (500 mg.) in hydrobromic acid–acetic acid (50%; 7 c.c.) was set aside for 48 hr. The *diacetyl-lactone* was obtained as needles (from methanol–acetone), (300 mg.), m. p. 226° (decomp.), $[\alpha]_D$ +132° (*c*, 0·83 in MeOH) (Found: C, 69·85; H, 8·7. $C_{34}H_{50}O_8$ requires C, 69·6; H, 8·6%). The compound did not give a colour with tetranitromethane.

(*b*) A 5% solution of bromine in acetic acid (25 c.c.) was added dropwise to a solution of barringtogenic acid (1·5 g.) and sodium acetate (4 g.) in acetic acid (90%; 30 c.c.). After 1 hr. the mixture was poured into water containing sodium thiosulphate (3 g.), and the product crystallised from methanol and acetone–methanol. A *bromolactone* was obtained as needles (1·1 g.), m. p. 239—240° (decomp.), $[\alpha]_D$ +147° (*c*, 0·34 in MeOH) (Found: Br, 13·8. $C_{30}H_{45}O_6Br$ requires Br, 13·75%).

Attempted Oxidation of Dimethyl Di-O-acetylbarrintogenate with Osmium Tetroxide.—Dimethyl barringtogenate diacetate was recovered after 10 days' treatment with osmium tetroxide in pyridine.

Reduction of Dimethyl Barringtogenate with Lithium Aluminium Hydride: Barringtogenol.—A solution of lithium aluminium hydride (1 g.) in dry ether (100 c.c.) was added to one of dimethyl barringtogenate (500 mg.), and the mixture stirred for 2 hr. The product was worked up in the usual way and crystallised from pyridine, giving needles (320 mg.), m. p. 286—287°, $[\alpha]_D$ +17° (*c*, 1·3 in pyridine) (Found, on sample dried at 150°: C, 75·7; H, 10·5. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). A mixture with natural barringtogenol of m. p. 290—291° had 288—289°; a mixture with the product, m. p. 286°, of the lithium aluminium hydride reduction of arjunolic acid had m. p. 288°. It readily formed a *tetra-acetate*, m. p. 269—270°, $[\alpha]_D$ +15° (*c*, 0·71 in pyridine) (Found, on sample dried at 150°: C, 70·8; H, 9·0. $C_{38}H_{58}O_8$ requires C, 71·0; H, 9·0%), which did not depress the m. p. of the tetra-acetate of natural barringtogenol.

Barringtogenol.—This triterpene (Found, on sample dried at 150°: C, 75·8, 75·8; H, 10·4, 10·4%) gave a cherry-red solution in sulphuric acid; Salkowsky reaction, acid layer deep orange; Liebermann–Burchardt reaction, pink, rapidly changing to violet, with strong fluorescence. It was unaffected by boiling 10% ethanolic potassium hydroxide. Reaction with perbenzoic acid (about 140 hr. were required for complete reaction) indicated the presence of one double bond. The number of 1 : 2-diol units was estimated with periodic acid in the usual way; the oxidation corresponded with 0·67, 0·97, and 0·99 unit after 3, 24, and 30 hr., respectively. A similar result was obtained by use of lead tetra-acetate.

The tetra-acetate (yield 70%), after chromatography and crystallisation from methanol–ether, formed small needles, m. p. 269—270°, $[\alpha]_D$ +15° (*c*, 2·06 in pyridine) (Found, on sample dried at 150°: C, 70·9, 70·9; H, 9·3, 9·1%). The *tetrabenzoate* after being chromatographed from benzene solution (alumina) and crystallised from methanol–ethyl acetate formed needles, m. p. 236—238°, $[\alpha]_D$ +10° (*c*, 0·86 in pyridine) (Found: C, 78·3; H, 7·4. $C_{58}H_{66}O_8$ requires C, 78·2; H, 7·5%). Treatment of barringtogenol (340 mg.) with a mixture of dry ether (200 c.c.), dry acetone (50 c.c.), and concentrated sulphuric acid (1 c.c.) gave the OO′-*isopropylidene derivative* (280 mg.), m. p. 150—154° (decomp.), $[\alpha]_D$ +20° (*c*, 1·2 in pyridine) (Found: C, 76·8; H, 10·5. $C_{33}H_{54}O_4$ requires C, 77·0; H, 10·6%).

Chromic Acid Oxidation of Barringtogenol: Dimethyl Didehydrobarringtogenate.—Barringtogenol (2·1 g.) was oxidised with chromic acid as described for barringtogenic acid. The acidic product was isolated as before, and purified by repeated precipitation from dilute methanol. The amorphous product (0·95 g.) (*M*, by titration with alkali, 492; *M*, by analysis of its silver salt, 496) was then esterified with diazomethane and the ester crystallised several times from ethyl acetate (charcoal). The dioxo-compound was obtained as fine needles (520 mg.), m. p. 219—220°, $[\alpha]_D$ +38° (*c*, 0·64 in pyridine) (Found: C, 72·9; H, 8·7%). It was identical with

that obtained from barringtogenic acid. Its dioxime, prepared as described before, had m. p. and mixed m. p. 287—289°, $[\alpha]_D$ +47° (*c*, 0·95 in pyridine) (Found: C, 69·3; H, 8·65%).

Pyrolysis of Barringtogenol.—Barringtogenol (1 g.) and finely divided copper (5 g.) were heated at 270° for 1 hr. The evolved gases were passed into a 2% solution of β-naphthol in 50% ethanol containing a few drops of concentrated hydrochloric acid. The solution gradually became turbid, and on gentle boiling, yielded a crystalline precipitate (63 mg.). This was recrystallised twice from dilute methanol and then melted at 187—188° (decomp.), undepressed by authentic di-2-naphthyloxymethane.

11 : 13(18)-*Dehydrobarringtogenol Tetra-acetate.*—Barringtogenol tetra-acetate (1·3 g.), selenium dioxide (2 g.), and acetic acid (20 c.c.) were heated under reflux for 6 hr. The product was worked up in the usual way and chromatographed in benzene on alumina. Elution with light petroleum and light petroleum–benzene gave 11 : 13(18)-*dehydrobarringtogenol tetra-acetate* as needles (from light petroleum–methanol) (250 mg.), m. p. 193—194°, $[\alpha]_D$ −60° (*c*, 1·8 in pyridine) (Found: C, 71·3; H, 8·7. $C_{38}H_{54}O_8$ requires C, 71·2; H, 8·8%). Light absorption in EtOH: max. 250, and 262 mμ; log ε 4·1 and 3·9.

The authors thank Professor F. E. King for a sample of the lithium aluminium hydride reduction product of arjunolic acid, Professor D. H. R. Barton for advice during the early stages of this work, and Dr. S. B. Rao who arranged for the infrared spectra to be determined.

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840. *The Identity of the Cubic Oxide Present in Films on Iron.*

By D. Eurof Davies and U. R. Evans.

Some doubt has been felt about the possibility of distinguishing members of the series of cubic iron oxides of which Fe_3O_4 and γ-Fe_2O_3 are end members. New experiments show that the additional lines characteristic of γ-Fe_2O_3 appear when the transformation Fe_3O_4 ⟶ γ-Fe_2O_3 is about 80% complete. Iron, heated in hydrogen (to destroy the original film) and then exposed to oxygen, develops films which are close to γ-Fe_2O_3 if formed at room temperature, but contain more iron if formed at higher temperatures, approaching Fe_3O_4.

It is still believed in some quarters that it is impossible to distinguish with certainty between the two cubic oxides, magnetite and γ-ferric oxide. In 1945, Verwey [1] stated that the patterns obtained by powder *X*-ray methods are too similar for a distinction to be made. Later, however, Rooksby [2] published *X*-ray photographs, bringing out definite differences between them.

It is indeed often thought that there is no way of knowing whether the invisible film formed on iron exposed to dry air at room temperatures is magnetite or γ-ferric oxide. In regard to films formed at higher temperatures, however, pronouncements have been made, based on slight differences of pattern which are known to exist. Vernon, Calnan, Clews, and Nurse,[3] studying oxidation at about 200°, found the film to be duplex, with rhombohedral α-Fe_2O_3 overlying cubic oxide; they used electron-diffraction examination of the films after stripping them from the metal; those workers who had examined the films on the metal had reported only α-Fe_2O_3. The two oxides Fe_3O_4 and γ-Fe_2O_3 are the end members of a continuous series of cubic solid solutions, the members having a magnetite structure with an increasing deficiency of iron. Vernon and his colleagues found that the cubic material formed at 225° initially has a composition near to γ-Fe_2O_3 but rather rapidly changes to Fe_3O_4; at 180° the change is slow, and even after 453 hours the composition

[1] Verwey, *Z. Krist.*, 1945, **91**, 66.
[2] Rooksby, Chapter X of Brindley's book "*X*-Ray Identification and Crystal Structures of Clay Minerals," Fig. X-3, opposite p. 257 (Mineralogical Society), 1951.
[3] Vernon, Calnan, Clews, and Nurse, *Proc. Roy. Soc.*, 1952, *A*, **216**, 375.

Fe_3O_4 is not reached. Moreau and Bardolle [4] state that the oxide present below the α-Fe_2O_3 is magnetite when formed at about 300°, and γ-Fe_2O_3 when formed at about 250°.

These investigations mainly concern high temperatures, although Vernon and his colleagues, on their schematic diagram, indicate the invisible film formed at room temperature as being " cubic, near to γ-Fe_2O_3." Mayne and Pryor [5] concluded from electron-diffraction and other experiments that film-free iron when immersed in potassium chromate or chromic acid solution at ordinary temperatures develops a film of γ-Fe_2O_3.

In the course of research on the kinetics of oxidation,[6] it was found possible to distinguish between the end members of the series by *X*-rays. The results, which were not included in the original paper, are as follows :

(1) *X-Ray Studies of Powders.*—It seemed important to ascertain the point at which the distinguishing features of γ-Fe_2O_3 appear. Accordingly, *X*-ray powder photographs of γ-Fe_2O_3 and magnetite were prepared. These showed small but definite differences. The lines corresponding to the spacings, 3·72, 3·40, 2·77, 2·64, 2·32, and 2·24 Å appeared in the γ-Fe_2O_3, but not in the magnetite, photographs. Again, there was a noticeable shift of the lines towards the high-angle end of the γ-Fe_2O_3 pattern, owing to a small difference in lattice parameter.

These results confirm Rooksby's and show that it is possible to distinguish with confidence between the two compounds. The magnetite used for the powder photographs was obtained from two sources, and although the pattern obtained from both samples was identical, the ferrous content was slightly different—neither being exactly the theoretical value. When this magnetite was heated at 400° the ferrous content decreased, and when the transformation to γ-Fe_2O_3 was about 80% complete, the additional lines could be seen.

(2) *Electron-diffraction Studies of High-temperature Films.*—The iron used contained C, 0·034; Si, 0·010; Mn, 0·145; S, 0·015; P, 0·032; Ni, 0·030; Cr, 0·007; and Mo, 0·005%. It was first heated in hydrogen to destroy the invisible film, and then in oxygen. The visible films thus obtained were stripped by the alcoholic iodine method and examined by (i) *X*-rays, (ii) electron diffraction (transmission method, applied to the stripped film). In addition, electron-diffraction reflection studies were made of the film on the metal, except in the case of films formed at 175°, where the rings were too diffuse. The patterns showed that the films formed at 175° and 225° consisted of α-Fe_2O_3 alone, and those formed at 300° contained α-Fe_2O_3 along with cubic oxide (this was also true of films formed at 175° on abraded, as opposed to hydrogen-treated, iron). At 250° the films were α-Fe_2O_3 alone after 2 hr., but α-Fe_2O_3 with cubic oxide after 10 hr. No lines of metallic iron were found in any case. The cubic oxide may have been magnetite or any phase between magnetite and 80% Fe_2O_3.

The results were confirmed by gravimetric and electrometric measurements, and by chemical examination of the films. The fact that the inner layer of the duplex film was not γ-Fe_2O_3 but a cubic oxide containing ferrous iron was shown by destroying the α-Fe_2O_3 by reductive dissolution [7] and stripping the remaining film in alcoholic iodine. It was found to be magnetic, and chemical tests showed it to contain ferrous iron as well as ferric.

(3) *Electron-diffraction Studies of Low-temperature Films.*—Electron-diffraction was applied to a specimen heated in hydrogen, cooled, and then exposed to oxygen at room temperature, but the reflection pattern was *diffuse*. A transmission photograph of the film stripped from such a specimen was still too diffuse, but after vacuum annealing at 360° for 1 hr. the pattern became *sharp* and contained the extra rings first observed in the *X*-ray pattern of γ-Fe_2O_3. To ascertain whether the ferric oxide might have been formed by oxidation of Fe_3O_4 owing to traces of oxygen, experiments were carried out by heating films in air. This, however, produced the rings of α-Fe_2O_3 (the form stable at the annealing temperature). It is concluded that the air-formed film is either γ-Fe_2O_3 or a cubic oxide, the composition of which lies between 80% Fe_2O_3 and γ-Fe_2O_3.

Dr. J. E. O. Mayne has kindly made the following observation : " The conclusion

[4] Moreau and Bardolle, *Compt. rend.*, 1955, **240**, 520.
[5] Mayne and Pryor, *J.*, 1949, 1831.
[6] Davies, Evans, and Agar, *Proc. Roy. Soc.*, 1954, *A*, **225**, 443.
[7] Pryor and Evans, *J.*, 1950, 1259—1276.

regarding the composition of the air-formed film is based on the assumption that the fragments of stripped film did not change in composition when they recrystallized during vacuum annealing at 360°.

" Either, or both, of the following changes could have occurred : (i) *Oxidation.* It has recently been found, by Hancock,[8] that the air-formed film thickened by 10% when heated in a vacuum at 70° for 6 hr. This may have been due to residual oxygen, or to adsorbed air evolved from the heated glass walls. (ii) *Reduction.* Evans,[9] who first isolated the air-formed film, noted that it frequently contained small particles of metallic iron. This has been confirmed by the observation that portions of films stripped from passivated specimens frequently developed rusty spots after storage for some months in methanol. These particles of iron might have taken part in the recrystallization during annealing."

The authors appreciate these possibilities, but the effect of oxygen or iron traces had not been overlooked. Oxygen was found to convert magnetite into α-ferric oxide, the stable form, as stated above; the existence of γ-ferric oxide in the film cannot, therefore, be explained in that way.

The presence or absence of metallic iron in films from abraded iron was found in early work [10] to depend on the level at which films are undermined. It is less likely to occur in films from unabraded specimens, and appears to be absent from the films studied, since no iron lines could be seen. Had it been present, it might have reduced ferric oxide to magnetite; it could hardly have changed magnetite to ferric oxide.

The authors thank Dr. R. K. Hart for carrying out the electron-diffraction examinations; Dr. J. P. Chilton for help with the film stripping; Dr. W. H. J. Vernon for constructive suggestions; and Dr. W. H. Taylor and Dr. P. B. Hirsch for helpful discussion of the *X*-ray data.

Department of Metallurgy, Cambridge. [*Received, May 9th,* 1956.]

[8] Hancock, unpublished work.
[9] Evans, *J.*, 1927, 1020.
[10] Evans and Stockdale, *J.*, 1929, 2651.

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841. *Four-, Five-, and Six-covalent Palladium*(II) *Complexes with a Di(tertiary) Arsine.*

By C. M. Harris and R. S. Nyholm.

The complexes formed by bivalent palladium with the chelate group *o*-phenylene-bis(dimethylarsine) (termed " as " below) have been investigated. The following compounds have been prepared and studied: $PdX_2,2as$ where X = Cl, Br, I, CNS, NO_3, and ClO_4. Molecular conductivities together with conductometric titrations and spectrophotometric absorption studies lead to the conclusion that the colourless diperchlorate is undoubtedly the four-covalent salt, $[Pd\ as_2](ClO_4)_2$, whereas the other compounds, which are highly coloured, behave as five-covalent complex salts of the type $[Pd\ as_2X]X$ in non-aqueous ionising solvents such as nitrobenzene. The reaction, $[Pd\ as_2]^{++} + X^- \longrightarrow [Pd\ as_2X]^+$, where X = Cl, Br, or I, is shown to be quantitative in nitrobenzene. By this reaction the halogeno-perchlorates $[Pd\ as_2X]ClO_4$ (X = Cl, Br, and I) have been prepared from acetone solution. These are typical uni-univalent electrolytes in nitrobenzene. Evidence is presented to support a distorted octahedral structure for $Pdas_2I_2$ in the solid state.

The stereochemistry of bivalent palladium is characterised by the square arrangement in all its four-covalent complexes. This arrangement has been shown by *X*-ray crystallography to occur, for example, in the salt-like complexes $K_2[PdCl_4]$ [1] and $[Pd(NH_3)_4]Cl_2,H_2O$ [2]

* The authors are grateful to the referees for drawing their attention to this work.

[1] Dickinson, *J. Amer. Chem., Soc.* 1922, **44**, 2404.
[2] Dickinson, *Z. Krist.* 1934, **88**, 281.

and in the non-electrolytes $[(NH_3)_2PdC_2O_4]$[9] and *trans*-$[(NH_3)_2PdI_2]$.[3] A similar arrangement has been observed in binuclear complexes in which the palladium atom is four-covalent, *e.g.*, $[PdCl_2,Et_3As]_2$.[4] The square arrangement in four-covalent palladium(II) complexes is considered by Pauling [5] to arise from the use of $4d5s5p^2$ hybrid bonds (see Fig. 1). This also explains the diamagnetism of all known palladium(II) complexes.

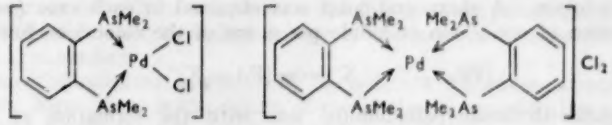
FIG. 1. *Electronic configuration of palladium complexes.*

The co-ordination number six has been reported in a few unusual complexes whose structures have been little investigated. Thus, in the unstable trichelate diazoamino-complexes of palladium prepared by Dwyer,[6] and in di-(1 : 2 : 3-triaminopropane)palladium(II) iodide,[7] the palladium atom is presumably six-covalent if all donor atoms are linked to the metal atom. The structure of the black compound [8] of empirical formula $Pd(NH_3)_2Cl_2$ has recently been examined by Cohen and Davidson [9] who suggest that it is similar to that of the corresponding platinum compound $Pt(NH_3)_2Br_2$, the structure of which has been determined by *X*-ray crystallography.[10] The deeply coloured platinum compound contains equal numbers of square $Pt^{II}(NH_3)_2Br_2$ and octahedral $Pt^{IV}(NH_3)_2Br_4$ molecules. These are arranged in chains so that the Pt^{II} atoms form two additional weak bonds with bromide atoms of the Pt^{IV} molecules.

The isolation of five-covalent Pd(II) complexes does not appear to have been reported previously although evidence for the occurrence of five-covalent Pd(II) in aqueous solution has been put forward. Thus in spectrophotometric studies Sandaram and Sandell * [11] observed that an interaction between $[PdCl_4]^{2-}$ and Cl^- ions occurs in aqueous solution and they cautiously inferred that $[PdCl_5]^{3-}$ and $[PdCl_6]^{4-}$ ions were formed. It is interesting that Pauling [5] suggested that square co-ordinated Ni(II), Pd(II), and Pt(II) might conceivably form five-covalent complexes by utilising the single vacant 4*p*, 5*p*, or 6*p* orbital of the metal atom respectively. After some observations on the ditertiary arsine complexes of tervalent gold [12] and the behaviour of bivalent nickel with a tritertiary arsine,[13] the complexes of palladium(II) with the diarsine o-$C_6H_4(AsMe_2)_2$ (termed "as" in short formulæ below) have been reinvestigated with the above idea in mind. Some years ago Chatt and Mann,[14] who first studied this chelate group, prepared two complexes of palladium with the diarsine and assigned to them the structures (I) and (II), the former being a non-electrolyte. These workers noted that the compound (II), when recrystallised from water, yielded an almost colourless compound which rapidly changed to a deep yellow one, presumably owing to a loss of water of crystallisation. This change seemed interesting, particularly since palladium tetrammines are usually colourless, whereas chloropalladium(II) compounds (containing a Pd–Cl bond), as in (I), are often yellow. Further information was obtained on adding iodide ions to an aqueous solution of $PdCl_2,as_2$. An orange monohydrate, $PdI_2,2as,H_2O$, was precipitated at once; this was converted into

[3] Mann, Crowfoot, Gattiker, and Wooster, *J.*, 1935, 1642.
[4] Mann and Wells, *J.*, 1938, 702; Wells, *Proc. Roy. Soc.*, 1938, *B*, **167**, 169.
[5] Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, 2nd Edn., 1948, pp. 98—103.
[6] Dwyer, *J. Amer. Chem. Soc.*, 1941, **63**, 78.
[7] Mann, *J.*, 1929, 656.
[8] Drew, Pinkard, Preston, and Wardlaw, *J.*, 1932, 1895.
[9] Cohen and Davidson, *J. Amer. Chem. Soc.*, 1951, **73**, 1955.
[10] Brosset, *Arkiv Kemi, Min., Geol.*, 1948, **25**, No. 19.
[11] Sunderam and Sandell, *J. Amer. Chem. Soc.*, 1955, **77**, 855.
[12] Harris and Nyholm, unpublished work; Harris, Ph.D. Thesis, 1955, New South Wales; Harris, Nyholm, and Stephenson, *Rec. Trav. chim.*, 1956, **75**, 687.
[13] Barclay and Nyholm, *Chem. and Ind.*, 1953, 378.
[14] Chatt and Mann, *J.*, 1939, 1622.

the deep red anhydrous compound by refluxing it with acetone. This red iodide, PdI_2,as_2, gave a reddish solution in nitrobenzene. The molecular conductivities of the bis(diarsine)-palladium(II) chloride and iodide and later the orange bromide indicated that those compounds function as uni-univalent electrolytes in nitrobenzene solution (see Table 1); for



comparison, Table 2 lists the molecular conductivities of a considerable number of compounds in this solvent. These figures, together with the observed marked difference in colour between $[Pd\ as_2][ClO_4]_2$, the cation of which is colourless, and the compound $Pd\ as_2I_2$ which is red both in the solid state and in nitrobenzene solution, suggested that part of the halogen is covalently bound to the palladium atom even in nitrobenzene. The perchlorate,

TABLE 1. *Molecular conductivities of palladium–diarsine complexes in nitrobenzene at 25°.*

Compound	Colour	Molar concn. ($\times 10^4$)	Mol. conductivity (mho)	Compound	Colour	Molar concn. ($\times 10^4$)	Mol. conductivity (mho)
$[Pd\ as_2](ClO_4)_2$	Colourless	4·1	46·2	$[Pd\ as_2I]I$	Red	5·5	26·9
$[Pd\ as_2Cl]Cl$ ...	Deep yellow	5·7	25·7	$[Pd\ as_2I]ClO_4$	Red	5·6	27·9
$[Pd\ as_2Cl]ClO_4$...	Deep yellow	5·3	29·0	$[Pd\ as_2NO_3]NO_3$	Orange	2·3	25·5
$[Pd\ as_2Br]Br$ ...	Orange	5·1	25·1	$[Pd\ as_2CNS]CNS$	Yellow	2·8	30·0
$[Pd\ as_2Br]ClO_4$	Orange	5·4	25·4				

TABLE 2. *Summary of the molecular conductivities of various complexes in nitrobenzene solution.*

Compound	Molar concn. ($\times 10^4$)	Temp.	Mol. conductivity
$[Cu\ as_2]X$ [a] (X = ClO_4, Br, I, $CuCl_3$, $CuBr_2$)	9·2—1·75	25°	23·3—29·4
$[Au\ as_2]X$ [b] (X = ClO_3, Br, I, picrate, AuI_2, CuI_2)	8·2—2·5	20	22·1—27·4
$[Cu(phen)_2]X$ [b] (X = ClO_4, I, CNS)	10—2·5	20	25·0—29·4
$[Cu(dipy)_2]ClO_4$ [b]	10	20	27·7
$[Cu(AsPh_2Me)_4]ClO_4$ [c]	39	25	24·4
[phen H][AuX$_4$] [b] (X = Cl, Br)	10—12·3	25	29·7—33·0
$[Au(phen)X_2]ClO_4$ [b] (X = Cl, Br)	10—2·5	25	33·0—33·1
$[Au(dipy)Cl_2]ClO_4$ [b]	8·0	25	33·7
$[Au(py)_2Br_2]ClO_4$ [b]	5·0	25	30·5
$[Au(phen)X_2][AuX_4]$ [b] (X = Cl, Br)	5·7—7·0	25	27·1—27·7
[dipy, Au, Et_2][$AuEt_2Br_2$] [d]	28—2	25	24·6—26·7
$[Fe(dipy)_3]I_2$ [b]	2·5	20	57·8
$[Cu(phen)_2](ClO_4)_2$ [b]	5·0	25	43·1
$[Cu(AsPh_2MeO)_4](ClO_4)_2$ [e]	36·3	25	38·6
$[Co(triarsine)_2](ClO_4)_2$ [f]	12	25	44·9

[a] Kabesh and Nyholm, *J.*, 1951, 38. [b] Harris, "Researches on the Co-ordination Compounds of the Group IB Elements and Related Compounds," Ph.D. Thesis, New South Wales, 1955. [c] Nyholm, *J.*, 1952, 1257. [d] Foss and Gibson, *J.*, 1949, 3063. [e] Nyholm, *J.*, 1951, 1767. [f] Barclay and Nyholm, *Chem. and Ind.*, 1953, 378.

$Pd(ClO_4)_2,as_2$, was then prepared by treating an aqueous solution of the chloride with perchloric acid. This compound, which is colourless, is undoubtedly the four-covalent palladium(II) complex $[Pd\ as_2](ClO_4)_2$; its molecular conductivity is approximately double those of the halides (Table 1).

Thus, it seemed likely that the halide compounds PdX_2,as_2 (X = Cl, Br, or I) could well be five-covalent complexes of the type $[Pd\ as_2X]X$ in nitrobenzene solution.

In keeping with this was the fact that addition of halide ions to a nitrobenzene or acetone solution of the colourless perchlorate, $[Pd\,as_2](ClO_4)_2$, resulted in an immediate colour change ranging from yellow for chloride ions to reddish-brown in the case of iodide ions. This was confirmed by titrating conductometrically the di-(*o*-phenylenebisdimethylarsine)-palladium(II) ion, in the form of the perchlorate, with halide ions (Cl^-, Br^-, and I^-) in nitrobenzene solution. A sharp end-point was obtained in each case (see Figs. 2—4) after the addition of one g.-ion of halide per g.-ion of the colourless four-covalent di-

$$[Pd\,as_2]^{++} + X^- \longrightarrow [Pd\,as_2X]^+$$

(*o*-phenylenebisdimethylarsine)palladium(II) ion, with the formation of the coloured halogenodi-(*o*-phenylenebisdimethylarsine)palladium(II) ion. By using this reaction we succeeded in isolating the coloured crystalline perchlorates, $[Pd\,as_2X]ClO_4$ [X = Cl (yellow), Br (orange) and I (deep red)], from acetone solution. The molecular conductivities of these perchlorates (see Table 1) were similar to those of the halides and in keeping with those of other uni-univalent electrolytes in nitrobenzene solution.

Conductometric titrations of $[Pd\,as_2](ClO_4)_2$ (100 *ml. of* 5×10^{-4}M-*solution*) *with halide ions in nitrobenzene at* 25°.

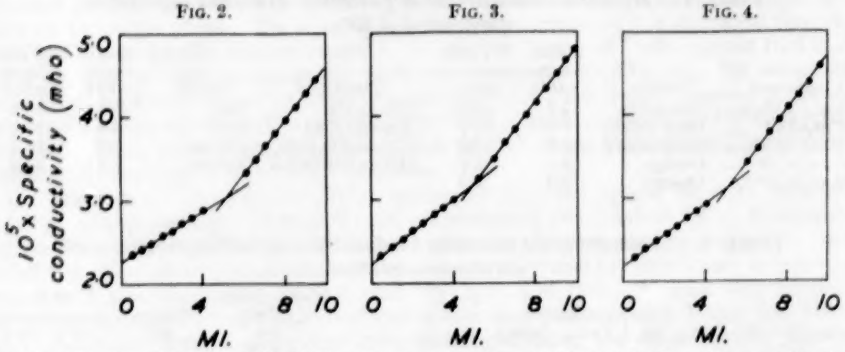


FIG. 2: *Titration with* 10^{-2}M-$AsPh_3MeCl$. FIG. 3: *Titration with* 10^{-2}M-NEt_4Br. FIG. 4: *Titration with* 10^{-2}M-1-*methylquinolinium iodide*. (*Conductivities corrected for dilution.*)

The monoiododi-(*o*-phenylenebisdimethylarsine)palladium(II) ion is suitably coloured for spectrophotometric measurements in nitrobenzene solution and has an absorption maximum in this solvent at 4300 Å (Fig. 5). The colourless di-(*o*-phenylenebisdimethylarsine)palladium(II) ion does not absorb at this wavelength and, by applying the methods of continuous variation to mixtures of the $[Pd\,as_2]^{++}$ ion and iodide ions in nitrobenzene, the curve in Fig. 6 was obtained. This shows that $[Pd\,as_2]^{++}$ ions and iodide ions react together giving a maximum optical density at a wavelength of 4300 Å, when these ions are in a 1 : 1 ratio. This confirms the results of the conductometric titrations.

The orange nitro-compound, $Pd(NO_2)_2$,2Diarsine, and the yellow thiocyanato-complex, $Pd(CNS)_2$,2Diarsine, were prepared from aqueous solutions of the chloride by double decomposition. They also function as uni-univalent electrolytes in nitrobenzene solution.

It is interesting that the yellow chloro-compound, $PdCl_2$,2Diarsine, dissolves readily in water to a colourless solution containing $[Pd\,as_2]^{++}$ ions which give a precipitate of the di-perchlorate, $[Pd\,as_2](ClO_4)_2$, on the addition of perchloric acid. This presumably arises from the removal of covalently bound chlorine because of hydration effects: $[Pd\,as_2Cl]^+ \rightleftharpoons [Pd\,as_2]^{++} + Cl^-$. The fact that this equilibrium occurs in dilute aqueous solution is reflected in the molecular conductivity of the chloride ($\Lambda_M = 180$ mho in $0{\cdot}88 \times 10^{-3}$M-solution at 19°). The orange bromo-complex, $Pd\,as_2Br_2$, undergoes an analogous change in water, forming a colourless solution with a similar conductivity ($\Lambda_M = 168$ mho in 10^{-3}M-solution at 21°). The red iodo-complex is almost insoluble in cold water

and hence its conductivity could not be measured. It dissolves in boiling water, however, forming a pale orange solution owing to the presence of $[Pd\ as_2I]^+$ ions. The red perchlorate $[Pd\ as_2I]ClO_4$ is precipitated on dropwise addition of perchloric acid. If a large excess of perchloric acid is added all at once the mixed compound $[Pd\ as_2](ClO_4)_2$, $[Pd\ as_2I]ClO_4$, is precipitated as deep yellow needles. The fact that the iodine atom appears to be more difficult to remove from the five-covalent palladium atom in aqueous solution parallels the lower hydration energy of the iodide ion compared with that for chloride and bromide ions.

Some interesting questions are posed by the isolation of these apparently five-covalent complex ions. First, there is the nature of the binding; secondly, the probable stereochemistry; and finally the question as to why such compounds do not appear to have been isolated previously. Provided that suitable bonding orbitals are available, the main factors which seem to limit the co-ordination number of a metal atom are (i) steric effects and (ii) the resulting charge on the metal ion. The existence of six-covalent Pd(IV) complex ions [in which the Pd(IV) atom must be even smaller than Pd(II)] suggests that

FIG. 5. *Absorption spectrum of iododi-(o-phenylenebisdimethylarsine)palladium*(II) *iodide* ($4{\cdot}63 \times 10^{-4}$M *in nitrobenzene*).

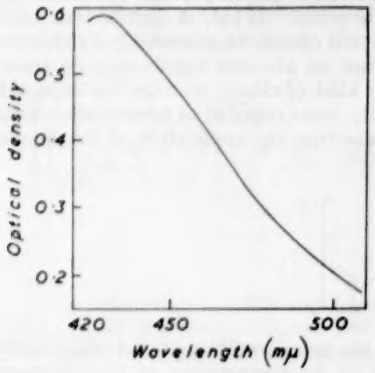
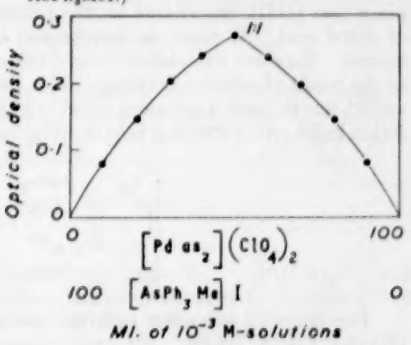


FIG. 6. *Continuous variation study of the reaction*, $[Pd\ as_2]^{++} + I^- \longrightarrow [Pd\ as_2I]^+$, *in nitrobenzene at* 430 mμ (0·5 *cm. cell*). (Optical density corrected for absorption by $AsPh_3MeI$.)

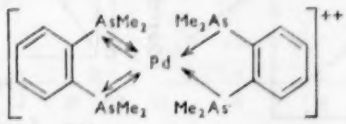


steric factors are not significant when using simple ligands. However, the second factor is apparently of greater importance. In the electroneutrality principle, Pauling [15] suggests that metal atoms tend to have charges of zero or at most between +1 and −1 unit. For metals a slight positive charge is more likely than a negative one. Hence ligands likely to leave the Pd(II) atom with a high negative charge are not favourable for increasing the co-ordination number. In order that the Pd(II) atom should not acquire too high a negative charge one could use ligands of high electronegativity (*e.g.*, Cl^-) which tend to form polar covalent bonds, most of the electron density due to the presence of the bonding σ electron pair being located on the ligand. This, for example, is presumably why fluoride ions form an $[FeF_6]^{3-}$ ion whereas the $[FeCl_4]^-$ ion is the more stable species with the chloride ion as ligand. Another means by which the metal atom could acquire a positive charge—or decrease its negative charge—would be for it to form double bonds to the ligand using *d* electron pairs of the metal atom. It will be noted that in this work we have made use of a ligand involving As(III), which, we believe, has a high capacity for double-bond formation. Also the fact that there is the maximum possible charge of +2 units on the $[Pd\ as_2]^{2+}$ cation is expected to facilitate the addition of the halide ion. Finally, in the case of the chloro-complex at least, the existence in nitrobenzene is presumably attributable partly to the lower solvation energy of nitrobenzene than of water;

[15] Pauling, "Victor Henri Memorial Volume," Liège, 1948, p. 8; *J.*, 1948, 1461.

water would tend to break the Pd–Cl bond more readily because of the hydration energy of the chloride ion.

If it is assumed that the formation of this type of five-covalent complex involves the use of the empty *5p* orbital by a pair of electrons from the ligand (*e.g.*, an iodide ion) we suggest that the conditions most likely to favour the addition of the negatively charged ligand is the *size of the positive charge* on the palladium. In the $[Pd(NH_3)_4]^{++}$ ion, the palladium receives a share of eight electrons, the distribution between the Pd and the N atoms being dependent on their electronegativities. If sharing were equal, the Pd(II) atom would have a formal charge of −2 units, but taking reasonable values for the electronegativities of palladium and nitrogen (1·5 and 3·0 respectively) we arrive at a figure of approximately −0·6 unit of charge (see Pauling [16]). Double bonding involving the use of $4d_\epsilon$ electron pairs of palladium to form a $d\pi$ bond to nitrogen in an ion such as $[Pd(NH_3)_4]^{++}$ is not feasible since the nitrogen has no vacant orbital. With these diarsine compounds, however, the arsenic atom has vacant *d* orbitals capable of forming such a π bond and for reasons discussed elsewhere (see Craig *et al.*[17]) such π bonding is expected. If the structure involved only *single* bonds between palladium and arsenic [four ordinary σ bonds of the type As ⟶ Pd; see (II)], then, reasonable values being assumed for the electronegativities of arsenic (2·0) and palladium (1·5), the charge on the palladium atom is expected to be about −1·6 units of charge. Craig *et al.*[17] have shown that in a square complex a maximum of two strong π bonds (at right angles) is expected to occur. If this is assumed to take place [see (III)], the charge on the palladium atom will change to something of the order of +0·6 unit. It must be emphasised that we place no absolute significance on these figures: they are calculated simply to establish the kind of charge distribution expected as the result of added π bonding. This change is in the sense required to favour union with an X^- ion to form a covalent bond. It follows from either the application of the simple Fajan rules or the Pauling neutrality principle.[15]



(III)

The effect of solvation calls for comment. In the reaction $[Pd\,as_2X]^+ + nH_2O \rightleftharpoons [Pd\,as_2]^{++} + X^-(H_2O)_n$, the two opposing tendencies in comparisons of the different anions (Cl^-, Br^-, I^-) are the Pd–X bond strength (to the fifth position) and the hydration energy of the X^- anion. The latter increases in the sequence $I^- < Br^- < Cl^-$ and hence, since the order of stability * in water is Pd–I > Pd–Br > Pd–Cl, it is concluded that the hydration energy increases more rapidly in the sequence $I^- < Br^- < Cl^-$ than does the bond energy Pd–I < Pd–Br < Pd–Cl.

Assuming that the square arrangement of the palladium and four arsenic atoms remains unaltered, then from a consideration of the position of the vacant *p* orbital one might expect a square pyramidal arrangement in the $[Pd\,as_2X]^+$ ion with the X^- group utilising the vacant *5p* orbital normal to the plane containing the palladium and arsenic atoms. Kimball [18] predicted the trigonal bipyramid for the use of one *s*, three *p*, and one *d* orbital † as in gaseous PCl_5.[19] Daudel and Bucher [20] have however pointed out that a square pyramidal arrangement should result if, in the combination dsp^2, the *d* orbital has a lower energy (*e.g.*, has a lower principal quantum number) than the *s* and *p* orbitals. This also

* The term "stability," used here, refers to free energy (ΔG) of dissociation in water. It does not necessarily parallel bond energy.

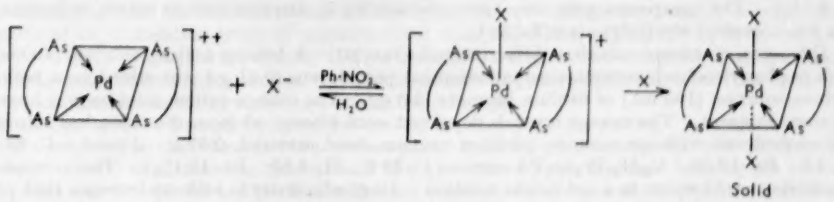
† Kimball did not distinguish between the cases where the *d* orbitals were in the lower or upper energy levels, *i.e.* $(n-1)dnsnp^2$ and $nsnp^2nd$.

[16] Ref. 5, p. 70.
[17] Craig, Maccoll, Nyholm, Orgel, and Sutton, *J.*, 1954, 332, and references contained therein.
[18] Kimball, *J. Chem. Phys.*, 1940, **8**, 194.
[19] Brockway and Beach, *J. Amer. Chem. Soc.*, 1938, **60**, 1836; Rouault, *Compt. rend.*, 1938, **207**, 620.
[20] Daudel and Bucher, *J. Chim. phys.*, 1945, **42**, 6.

follows from the group theory approach.[21] Jensen and Nygaard [22] have concluded from electric-dipole measurements that the square pyramidal arrangement does indeed occur in $NiBr_2,2Et_3P$ in which they believe that $3d4s4p^3$ bonds are present. The pentacarbonyl, $Fe(CO)_5$, on the other hand, has been shown by Ewens and Lister [23] to possess a trigonal bipyramidal arrangement even though the expected hybridisation involves $3d4s4p^3$ orbitals.

Although the compounds $PdX_2,2Diarsine$ (where X = Cl, Br, I, NO_2, and SCN) function as uni-univalent electrolytes $[Pd\ as_2X]^+X^-$ in nitrobenzene solution they apparently do not possess this structure in the solid state. Single crystals of the iodide have been examined by *X*-ray crystallography by Mr. N. C. Stephenson and shown to consist of discrete molecules of $Pd\ as_2I_2$ with elongated Pd–I bonds in the *trans*-octahedral positions. This compound is isomorphous with the corresponding bivalent platinum and nickel compounds and their structures will be discussed in detail in a forthcoming paper.[24] This type of octahedral complex may be considered to arise from the use of four square $4d5s5p^2$ bonds and two longer $5p5d$ bonds (in the case of palladium) normal to the plane.*

The nature of these palladium–diarsine complexes is at present best explained by the equilibria in the annexed sketch, involving four-, five-, and six-covalent palladium(II). It remains to be seen from crystal-structure determinations whether the apparently five-covalent ion, $[Pd\ as_2X]^+$, persists in the solid state. The structure of compounds of the type $[M\ as_2X]ClO_4$ (where $M = Pd^{II}$, Pt^{II}, and Ni^{II} and X = halogen) is now being studied in collaboration with Mr. Stephenson.



It is interesting that the rapid exchange of ligand with $[Ni(CN)_4]^{2-}$, $[Pt(CN)_4]^{2-}$, and $[PtX_4]^{2-}$, as shown by exchange and kinetic studies, has been thought to involve a five co-ordinated transition state employing the outer " *p* " orbital of the metal.[25]

Experimental

Di-(o-phenylenebisdimethylarsine)palladium(II) *Perchlorate.*—A solution of the chloride was prepared by heating together an alcoholic solution (16 ml.) of *o*-phenylenebisdimethylarsine (2·67 g.) with potassium tetrachloropalladate (1·55 g.) in alcohol (30 ml.) and water (16 ml.). The filtered solution was diluted with water (110 ml.), boiled, and treated dropwise with perchloric acid (73%). The colourless crystals which were immediately deposited were filtered from the hot solution and washed with hot water followed by cold acetone. This yielded 3·6 g. of vacuum-dried material [Found: C, 27·6; H, 4·0; Cl (as ClO_4^-), 8·2; Pd, 12·1. $C_{20}H_{32}O_8Cl_2As_4Pd$ requires C, 27·4; H, 3·7; Cl, 8·1; Pd, 12·15%]. The *compound* was sparingly soluble in hot acetone and nitrobenzene. In the latter solvent it functions as a bi-univalent electrolyte (see Table 1).

* Alternatively the shape can be interpreted by using ligand (crystal) field theory. A filled non-bonding d_{z^2} orbital is normal to the plane of the four square $4d5s5p^3$ bonds and this is expected to cause repulsion of the ligands along the *z* axis, *i.e.*, in the remaining two positions of the (distorted) octahedron. This is in accord with the fact that the two Pd–I bonds are longer than one would expect for a normal covalent bond.

[21] Craig, personal communication.
[22] Jensen and Nygaard *Acta Chem. Scand.*, 1949, **3**, 474.
[23] Ewens and Lister, *Trans. Faraday Soc.*, 1939, **35**, 681.
[24] Harris, Nyholm, and Stephenson, unpublished researches; see also *Nature*, 1956, **177**, 1127.
[25] Adamson, Welker, and Wright, *J. Amer. Chem. Soc.*, 1951, **73**, 4786; Taube, *Chem. Rev.*, 1952, **50**, 69.

Dichloro-di-(o-phenylenebisdimethylarsine)palladium(II).—An aqueous solution (5·0 ml.) of potassium tetrachloropalladate(II) (0·50 g.) was treated with alcohol (10 ml.), followed by an alcoholic solution (5·0 ml.) of *o*-phenylenebisdimethylarsine (0·89 g.), refluxed for about 10 min., filtered, and evaporated to dryness on a water-bath. A solution of the yellow residue in water (10 ml.) was evaporated to a small bulk and cooled in ice-water. The white crystals deposited were filtered off and washed with a small amount of ice-cold water followed by acetone. The acetone converted the white crystals (presumably a hydrate) into a yellow compound which was dried in a vacuum (P_2O_5) (yield 0·18 g.) (Found: C, 32·4; H, 4·2; Cl, 9·7. $C_{20}H_{32}Cl_2As_4Pd$ requires C, 32·0; H, 4·3; Cl, 9·5%). This *compound* is very soluble in cold water, sparingly soluble in nitrobenzene, and insoluble in acetone. Addition of perchloric acid to the filtrate gave 0·73 g. of di-(*o*-phenylenebisdimethylarsine)palladium(II) perchlorate.

This compound was more conveniently obtained by adding a solution of di-(*o*-phenylenebisdimethylarsine)palladium(II) perchlorate in boiling acetone to an acetone solution of excess of lithium chloride, and the yellow crystals deposited were washed with boiling acetone (Found: C, 31·8, 31·95; H, 4·3, 4·6; Cl, 9·6%). The compound functions as a uni-univalent electrolyte in nitrobenzene solution (see Table 1) but approaches the value of a bi-univalent electrolyte in aqueous solution (Λ_M = 180 mho in 0·88 × 10^{-3}M-solution at 19°).

Chlorodi-(o-phenylenebisdimethylarsine)palladium(II) *Perchlorate*.—A solution of di-(*o*-phenylenebisdimethylarsine)palladium(II) perchlorate (0·44 g.) in boiling acetone (400 ml.) was treated with an acetone solution (10 ml.) of lithium chloride (0·21 g./100 ml.). The resulting golden solution was evaporated to 100 ml. and kept at the b. p. for some time, deep yellow crystals being deposited. The *compound* was washed with hot acetone (yield of vacuum-dried material 0·09 g.) (Found: C, 29·05; H, 3·9; Cl, 8·7. $C_{20}H_{32}O_4Cl_2As_4Pd$ requires C, 29·5; H, 4·0; Cl, 8·7%). The compound was very sparingly soluble in nitrobenzene in which it functions as a uni-univalent electrolyte (see Table 1).

Dibromodi-(o-phenylenebisdimethylarsine)palladium(II).—A boiling acetone solution (400 ml.) of di-(*o*-phenylenebisdimethylarsine)palladium(II) perchlorate (0·41 g.) was added to a boiling acetone solution (100 ml.) of lithium bromide (3·0 g.). The orange-yellow solution was heated for some minutes. The orange crystals deposited were filtered off from the colourless solution and washed well with hot acetone (yield of vacuum-dried material, 0·37 g.) (Found: C, 28·7; H, 4·0; Br, 19·05. $C_{20}H_{32}Br_2As_4Pd$ requires C, 28·6; H, 3·85; Br, 19·1%). This *compound* is soluble in cold water to a colourless solution. Its conductivity is midway between that of a uni-univalent and a bi-univalent electrolyte in water (Λ_M = 168 mho in 10^{-3}M-solution 21°), although in nitrobenzene it functions as a uni-univalent electrolyte (Table 1).

Bromodi-(o-phenylenebisdimethylarsine)palladium(II) *Perchlorate*.—A boiling acetone solution (400 ml.) of di-(*o*-phenylenebisdimethylarsine)palladium(II) perchlorate (0·40 g.) was treated with an acetone solution (20·0 ml.) of lithium bromide (0·20 g./100 ml.) and evaporated to 150 ml., orange crystals being deposited. The solution was cooled and the *compound* filtered off and washed with cold acetone (yield, 0·15 g. of vacuum-dried material) (Found: C, 28·1; H, 3·9; Br, 9·6. $C_{20}H_{32}O_4ClBrAs_4Pd$ requires C, 28·0; H, 3·8; Br, 9·3%).

Di-iododi-(o-phenylenebisdimethylarsine)palladium(II).—A solution of *o*-phenylenebisdimethylarsine (1·14 g.) in alcohol (6 ml.) was added to potassium tetrachloropalladate(II) (0·66 g.) in water (10) ml.) and alcohol (20 ml.). The mixture was boiled for some minutes, diluted with water (100 ml.), and filtered at the b. p. into a solution of sodium iodide (3·0 g.) in hot water (30 ml.). The orange crystals deposited were filtered off and washed with cold water, then with absolute alcohol in which they were somewhat soluble to an orange-yellow solution. They appeared to be slowly becoming red (dehydration). On transference to acetone (50 ml.) and refluxing they were immediately converted into deep red (anhydrous) crystals. The red crystals were washed with cold acetone and dried under vacuum (yield 1·6 g.) (Found: C, 25·5, 25·5; H, 3·2, 3·4; I, 27·0; Pd, 11·3. $C_{20}H_{32}I_2As_4Pd$ requires C, 25·75; H, 3·5; I, 27·2; Pd, 11·4%). The *compound* is sparingly soluble in nitrobenzene in which it functions as a uni-univalent electrolyte (Table 1). It is insoluble in cold water but sparingly soluble at the b. p.

This compound was also isolated as an orange monohydrate by dissolving the anhydrous compound (0·25 g.) in boiling water (250 ml.) and adding the yellow solution with stirring, to a hot solution (30 ml.) of sodium iodide (2·0 g.). The orange needles were filtered off and washed with cold water, followed by dry ether, and dried at 120° (yield, 0·23 g. of orange crystals) (Found: I, 26·6. $C_{20}H_{34}OI_2As_4Pd$ requires I, 26·7%). Refluxing this *monohydrate* with acetone converted it into the red anhydrous compound.

Iododi-(o-phenylenebisdimethylarsine)palladium(II) *Perchlorate*.—A boiling acetone solution (400 ml.) of di-(*o*-phenylenebisdimethylarsine)palladium(II) perchlorate (0·48 g.) was treated

with an acetone solution (10·0 ml.) of sodium iodide (0·75 g./100 ml.), then evaporated to 100 ml., and the deep red crystals were filtered off and washed with boiling acetone (yield of vacuum-dried material, 0·14 g.) (Found: C, 26·35; H, 3·5; I, 14·0; Cl, 4·3. $C_{20}H_{33}O_4ClIAs_4Pd$ requires C, 26·5; H, 3·6; I, 14·0; Cl, 3·9%). This *compound* was sparingly soluble in nitrobenzene in which it functions as a uni-univalent electrolyte (see Table 1). It possessed $\chi_g = -0·22 \times 10^{-6}$ and is hence diamagnetic.

This salt was also obtained from Pd as_2I_2 as follows. A boiling aqueous solution (250 ml.) of the di-iodo-complex (0·20 g.), on dropwise addition of 72% perchloric acid (1·0 ml.), gave an immediate precipitate of the perchlorate. The compound was washed with hot water and cold acetone (yield of vacuum-dried material, 0·16 g.) (Found: C, 26·4; H, 3·5; I, 13·8; Cl, 4·3%).

The Mixed Compound Pd as_2IClO_4,Pd $as_2(ClO_4)_2$.—The iodide, Pd as_2I_2 (0·20 g.), was dissolved in boiling water (200 ml.) and treated rapidly with 72% perchloric acid (5·0 ml.). The yellow *perchlorate* deposited was filtered off, washed with cold water and cold absolute alcohol, and dried overnight in a vacuum (P_2O_5) (yield 0·16 g.) (Found: C, 26·6; H, 3·7; I, 7·0; Pd, 12·1. $C_{32}H_{40}O_{12}Cl_3IAs_4Pd$ requires C, 26·95; H, 3·6; I, 7·1; Pd, 12·0%). If the compound is washed with boiling water or cold acetone it is converted into the red compound [Pd as_2I]ClO_4.

Dinitrodi-(o-phenylenebisdimethylarsine)palladium(II).—A solution of the chloride was prepared by heating *o*-phenylenebisdimethylarsine (0·57 g.) with potassium tetrachloropalladate(II) (0·33 g.) in alcohol (8·0 ml.) and water (3·0 ml.). The filtered solution was diluted with water (25 ml.) and treated with sodium nitrite solution (6·0 g. in 10 ml.). On cooling to room temperature, a yellow crystalline *compound* was slowly deposited. This was filtered off, washed with small quantities of cold water, and then with large quantities of acetone. A further crop of crystals was obtained from the filtrate by adding more sodium nitrite (5·0 g.). When washed with acetone the crystals changed from light yellow to orange, presumably owing to loss of water of crystallisation (yield of vacuum-dried material, 0·23 g.) (Found: C, 31·2; H, 4·0; N, 3·7. $C_{20}H_{33}O_4N_2As_4Pd$ requires C, 31·2; H, 4·2; N, 3·6%). The compound was sparingly soluble in warm nitrobenzene in which it functions as a uni-univalent electrolyte (see Table 1). This compound is soluble in water to a colourless solution.

Dithiocyanatodi-(o-phenylenebisdimethylarsine)palladium(II).—A boiling solution of the chloride prepared as described in the previous paragraph was treated dropwise with an aqueous solution (15 ml.) of ammonium thiocyanate (2·0 g.). After a few minutes' heating the yellow precipitate was filtered off and washed with cold water followed by acetone (yield of vacuum-dried material, 0·67 g.) (Found: C, 33·2; H, 3·95; N, 3·4; Pd, 13·3. $C_{22}H_{33}N_2S_2As_4Pd$ requires C, 33·2; H, 4·1; N, 3·5; Pd, 13·4%). The *compound* is practically insoluble in water and sparingly soluble in warm nitrobenzene in which it functions as a uni-univalent electrolyte (Table 1).

Analyses.—Palladium. This could not be estimated by ignition to the metal owing to the presence of arsenic which tends to alloy with the palladium. The compound was decomposed by fuming with 36N-sulphuric acid (3 ml.) and drops of perchloric acid. After cooling and dilution with water the palladium was precipitated by dimethylglyoxime in the normal manner and the precipitate ignited to metallic palladium. The ignited metal was allowed to cool to room temperature in an atmosphere of methanol (filter-paper moistened with methanol held over mouth of crucible) to prevent the formation of palladium oxide.

Halogen (excluding perchlorate). Since the compound [Pd as_2]$(ClO_4)_2$ is soluble in hot dilute nitric acid the halogen (excluding chlorine from perchlorate) was determined gravimetrically as silver halide.

Other elements. Carbon and hydrogen were determined microanalytically by Dr. E. Challen. The chlorine in the form of perchlorate was determined by Dr. Zimmermann of the Australian Microanalytical Service, Division of Industrial Chemistry, C.S.I.R.O., Melbourne.

The authors thank Messrs. Garrett, Davidson, and Matthey (of Sydney) for the palladium used.

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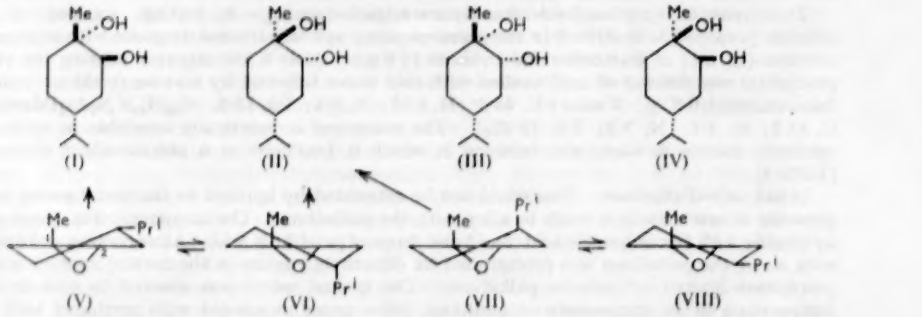
842. *Stereochemistry of cycloHexane Derivatives. Part IV.* Some Secondary Tertiary 1 : 2-Diols.*

By P. R. Jefferies and B. Milligan.

The hydroxylation of (±)-*p*-menth-1-ene is described and some evidence for the structures of the *trans*-diols is presented. Equilibration of a series of glycols with sodium in decalin is described and an explanation of some apparent anomalies is suggested. The rates of oxidation of the diols by periodate have been measured.

To provide a series of closely related secondary tertiary 1 : 2-diols we have examined the hydroxylation of (±)-*p*-menth-1-ene. Some details about the active diols are available,[1] but the racemic forms have not been described. Although the stereochemistry of the carvomenthols has not been completely clarified[2] we have adopted Bose's nomenclature,[3] and on this basis the menthols and carvomenthols are conformationally analogous. The *p*-menthane-1 : 2-diols are referred to as 1-hydroxycarvomenthols (I—IV). Hydroxylation of *p*-menth-1-ene by way of the epoxide or directly with peracetic acid gave mainly 1-hydroxy*neo*carvomenthol (I) and some 1-hydroxy*iso*carvomenthol (II). The production of a mixture of diols is expected on the basis of application[4] of the Fürst–Plattner[5] principle to rupture of the oxide mixture. The half-chair conformations (V, VI) of one oxide would undergo attack at positions 2 and 1, respectively. The conformation (V) will exist in larger proportion and will be attacked more readily than (VI) where attack at $C_{(1)}$ is hindered by both steric and inductive effects of the methyl group. This oxide should yield almost entirely 1-hydroxy*neo*carvomenthol (I), corresponding to rupture of form (V).



The oxide (VII, VIII) will be more stable in the form (VIII), but the rates of rupture could be similar since attack of epoxide (VIII) at $C_{(1)}$ is hindered by the methyl group and in form (VII) the approach to $C_{(2)}$ is hindered by the axial *iso*propyl group and a mixture of the diols (I) and (II) by rupture of conformations (VII) and (VIII), respectively, is expected.

Structures cannot be established by relation to (±)-carvomenthols or *p*-menthan-1-ols at present as no reliable information about these isomers exists. Hydroxylation of *p*-menth-1-ene with osmium tetroxide and esterification gave 1-hydroxy*neoiso*carvomenthol (IV) as the di-*p*-nitrobenzoate. Both *cis*-diols (III and IV) were obtained by hydroxylation

* Part III, *J.*, 1956, 2363.

[1] Schmidt, *Chem. Ber.*, 1949, **82**, 11; Meerwein, Ogait, Prang, and Serini, *J. praht. Chem.*, 1926, **113**, 9.

[2] Orloff, *Chem. Rev.*, 1954, **54**, 375.

[3] Bose, *Experientia*, 1952, **8**, 458.

[4] Bose, Chaudhuri, and Bhattacharyya, *Chem. and Ind.*, 1953, 869; Newth, *ibid.*, p. 1257; Cookson, *ibid.*, 1954, 223, 1512; Angyal, *ibid.*, p. 1230; Stevens and Dykstra, *J. Amer. Chem. Soc.*, 1953, **75**, 5975.

[5] Fürst and Scotoni, *Helv. Chim. Acta*, 1953, **36**, 1332, 1410.

by iodine–silver acetate–water,[6] or, less well, by *tert.*-butyl hydroperoxide [7] or by inversion of the bromohydrins derived from the epoxide mixture.[8] Much evidence for the configurations of the *cis*-diols is described in the following paper. The formation of the diol (IV) from osmium tetroxide follows attack *trans* to the *iso*propyl group although the product is less stable conformationally than the isomer (III).

The reduction of ketones with sodium and alcohol leads to the same mixture of alcohols as is obtained by direct equilibration with sodium,[9] the distribution of the isomers corresponding to their relative stability. We have been unable to obtain sufficient of the diol (III) to equilibrate it with sodium but the isomers (I), (II), and (IV) all yield the same product, 1-hydroxy*iso*carvomenthol (II), when treated in this way. Examination of the infrared spectrum of the equilibration product failed to indicate the presence of any other *p*-menthane-1 : 2-diol. As a model, the reaction was applied to the isomeric 1-methyl*cyclo*hexane-1 : 2-diols. The product was the *trans*-diol and no evidence for the presence of the *cis*-isomer could be obtained, indicating a close relation between the most stable conformations of 1-hydroxy*iso*carvomenthol and 1-methyl*cyclo*hexane-*trans*-1 : 2-diol. The inversion of configuration at $C_{(1)}$ in equilibration of (I) however is unexpected since tertiary alcohols are normally unaffected by the reaction,[10] which for secondary alcohols proceeds through ketonic intermediates. Without further experimental results it seems profitless to attempt to distinguish between possible mechanisms for this inversion at $C_{(1)}$. Although the equilibration product is 1-methyl*cyclo*hexane-*trans*-1 : 2-diol (IX; R = Me), yet if the size of the substituent is increased a stage will be reached where equilibration will yield the *cis*-diol (XI) as indicated for the 1-phenyl*cyclo*hexane-1 : 2-diols.[11] We accordingly extended the study to 1-ethyl- and 1-*iso*propyl-*cyclo*hexane-1 : 2-diols. The isomeric ethyldiols were prepared by standard methods. 2-Ethyl-2-hydroxy*cyclo*hexanone was obtained from a Grignard reaction with *cyclo*hexane-1 : 2-dione and was reduced with sodium and alcohol. The *trans*-isomer was isolated from this equilibrating reduction. Infrared analysis of the products from the sodium–decalin equilibration indicated at least 70% of *trans*-isomer. The 1-*iso*propyl*cyclo*hexane-1 : 2-diols were prepared in the usual manner and on equilibration afforded mainly the *cis*-diol. An attempt to gain a closer insight into these results was made by summing the energy differences between the *trans*-conformations (IX) and (X) and the *cis*-conformation (XI) by using the free-energy differences for groups in axial and equatorial positions at 39° recently given by Winstein and Holness,[12] allowing the approximate value 0·4 kcal./mole for the skew interaction between two hydroxyl groups and neglecting solvent effects. In the tabulated results no allowance is made for

Free energy differences (kcal./mole).

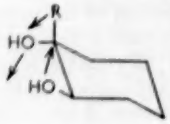
R	Me	Et	Pr^i
E_{IX-X}	0·6	0·9	>2·1
E_{IX-XI}	1·0	1·3	>2·5
E_{X-XI}	0·4	0·4	0·4

hydrogen bonding since this effect will not be present during equilibration. They show a stability order (XI) > (X) > (IX), regardless of the alkyl group. Although the nature of this equilibration is not fully understood it seems probable that the product will be the most stable disodium salt and not necessarily the most stable diol. Values of the free-energy difference between ONa in an axial and an equatorial position are unknown, but may be assumed to be rather larger than the value [12] (0·8 kcal./mole) for the hydroxyl group. As a result, conformation (IX) could be stabilised with respect to (X) and (XI) for the sodium salts derived from the *p*-menthane-, ethyl*cyclo*hexane-, and methyl*cyclo*hexane-1 : 2-diol. An electrostatic effect resulting in repulsion of the oxygen substituents would favour conformation (IX) over (XI) since the resultant deformation, indicated by arrows, would

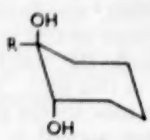
[6] Ginsburg, *J. Amer. Chem. Soc.*, 1953, **75**, 5746.
[7] Milas and Sussman, *ibid.*, 1936, **58**, 1302; 1937, **59**, 2345.
[8] Winstein and Buckles, *ibid.*, 1942, **64**, 2787.
[9] Vavon, *Bull. Soc. chim. France*, 1931, **49**, 937; Hückel, *Annalen*, 1937, **533**, 1.
[10] Stevens, *J. Amer. Chem. Soc.*, 1932, **54**, 3733; Doering, Cortes, and Knox, *ibid.*, 1947, **69**, 1700.
[11] Verkade, *Annalen*, 1928, **467**, 217.
[12] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

increase axial group interactions in the latter but decrease them in the former, corresponding to the reverse of the situation described by Angyal and Macdonald [13] for formation of cyclic complexes from *cis*- but not *trans*-1 : 2-diols.

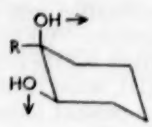
Dehydration of the four *p*-menthane-1 : 2-diols with dilute sulphuric acid gave a (±)-carvomenthone as the only identifiable product.



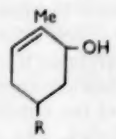
(IX)



(X)



(XI)



(XII)

The preparation of a (±)-carvotanacetol (XII; R = Pr^i) has been described previously.[14] Further examination of the products has provided the epimeric carvotanacetols, characterised by oxidation to carvotanacetone. The structure of the *trans*-isomer is indicated by its hydrogenation to a carvomenthol isolated by Johnston and Read [15] by similar treatment of (±)-*trans*-carveol (XII; R = CMe:CH$_2$). The assignment of the *trans*-configuration to the latter, originally based on the Auwers–Skita rule, is substantiated by its reactions.[2] Reaction of the mono-*p*-nitrobenzoates of both the diols (I) and (IV) with phosphorus oxychloride in pyridine gave the corresponding derivative of *trans*-carvotanacetol, providing evidence for the configurations of these two diols.

The rates of oxidation of some of the diols with periodate have been determined (see Table). The *cis*-diols are all oxidised faster than their *trans*-isomers and the very slow rate for 1-hydroxy*neo*carvomenthol is in agreement with a stable diaxial conformation.[16] The observed rate would correspond to presence of about 3% of the diequatorial conformation oxidising at the same rate as 1-hydroxy*iso*carvomenthol. The rates for two *p*-menthane-3 : 4-diols prepared by standard methods are included for comparison.

Rates of oxidation of diols with periodate at 25° (k_2 in mole^{-1} l. min.).

Diol	pH 10·5	pH 2	Diol	pH 10·5	pH 2
1-Hydroxy*neo*carvomenthol	~0·25	2·5	1-Methyl*cyclo*hexane-*trans*-1 : 2-diol	~2·0	60
1-Hydroxy*iso*carvomenthol	2·5	70	1-*iso*Propyl*cyclo*hexane-*cis*-1 : 2-diol	—	53
1-Hydroxycarvomenthol	6·5	—	,, ,, -*trans*- ,,	—	1·0
1-Hydroxy*neoiso*carvomenthol ...	8·8	—	*cis*-*p*-Menthane-3 : 4-diol	—	5·0
1-Methyl*cyclo*hexane-*cis*-1 : 2-diol	26	—	*trans*-*p*- ,, ,, ...	—	0·055

As a possible route to *p*-menthane-3 : 4-diols we have examined reduction of the 4-hydroxymenthone, prepared by Kötz and Steinhorst [17] by hydrolysis of 4-bromomenthone. *trans*-2-Hydroxymenthol was obtained by using sodium and alcohol. Rearrangement during hydrolysis of the bromide with production of 2-hydroxymenthone probably occurred.

Experimental

Unless otherwise stated alumina, type H from Messrs. P. Spence, was used for chromatography, and light petroleum had b. p. 60—70°. Microanalyses were by C.S.I.R.O. Microanalytical Laboratory, Melbourne.

trans-*Hydroxylation of* (±)-p-*Menth*-1-*ene*.—(±)-*p*-Menth-1-ene was prepared from dihydrocryptone.[14] (*a*) The hydrocarbon (23 g.) was treated with peracetic acid by the usual method, and the resulting monoacetates (16·5 g.) were hydrolysed with alkali. The crude diol gave fractions: (i) b. p. 98—128°/6·0 mm. (1·0 g.) and (ii) b. p. 128—132°/6·0 mm. (10·3 g.). Fraction (ii) yielded a partly crystalline *p*-nitrobenzoate. After being washed with light petroleum,

[13] Angyal and Macdonald, *J.*, 1952, 686.
[14] Macbeth, Milligan, and Shannon, *J.*, 1953, 2574.
[15] Read and Johnston, *J.*, 1935, 1138.
[16] Jefferies and Milligan, *J.*, 1956, 2363.
[17] Kötz and Steinhorst, *Annalen*, 1911, **379**, 13.

the crystalline ester (7·5 g.) was chromatographed in light petroleum–benzene (4 : 1; 150 c.c.) on alumina (150 g.). Elution with these solvents gave the *di*-p-*nitrobenzoate* of 1-hydroxy*iso*carvomenthol (1·20 g.) as pale yellow needles, m. p. 164°, after two crystallisations from methanol–chloroform (Found: C, 61·5; H, 5·4; N, 6·0. $C_{24}H_{24}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%). Benzene eluted the *di*-p-*nitrobenzoate* of 1-hydroxy*neo*carvomenthol (0·50 g.), needles (from methanol–chloroform), m. p. 185° (Found: C, 61·6; H, 5·6; N, 5·9%). The *mono*-p-*nitrobenzoate* of 1-hydroxy*neo*carvomenthol (2·00 g.) was eluted with ether–benzene (1 : 4). It crystallised as needles, m. p. 107°, from light petroleum (b. p. 40—60°) (Found: C, 63·9; H, 7·2; N, 4·5. $C_{17}H_{23}O_5N$ requires C, 63·6; H, 7·1; N, 4·4%).

(*b*) (±)-*p*-Menth-1-ene (18 g.) was added to ethereal monoperphthalic acid (1·1 mol.) and after 20 hr. the epoxide was isolated in the usual way and heated with water (60 ml.) at 120° during 3 hr. Isolation with ether and distillation gave a fraction (10 g.), b. p. 102—108°/0·4 mm. Crystallisation from hexane gave needles (6·7 g.) of 1-*hydroxy*neo*carvomenthol*, m. p. 77° (Found: C, 69·9; H, 11·7. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%). The *mono*-3 : 5-*dinitrobenzoate* crystallised from aqueous methanol as pale yellow plates, m. p. 51° (Found: C, 56·0; H, 6·0; N, 7·8. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·0; N, 7·7%). The *acetate* of the *p*-nitrobenzoate, prepared by use of boiling acetic anhydride, crystallised from aqueous methanol as plates, m. p. 107° (Found: C, 63·3; H, 6·9; N, 4·2. $C_{19}H_{23}O_6N$ requires C, 62·8; H, 6·9; N, 3·9%). The glycol isolated from the mother-liquors was esterified and the *p*-nitrobenzoates were separated as above into the di-*p*-nitrobenzoates of 1-hydroxy*neo*carvomenthol (0·2 g.) and of 1-hydroxy-*iso*carvomenthol (0·7 g.). Hydrolysis of the latter ester with methanolic potassium hydroxide gave 1-*hydroxy*iso*carvomenthol*, b. p. 118°/5 mm., m. p. 53° (Found: C, 70·3; H, 11·7%).

(*c*) A similar result was obtained when the epoxide mixture was shaken for 10 hr. with 5% aqueous perchloric acid.

cis-*Hydroxylation of* (±)-p-*Menth*-1-*ene*.—(*a*) The hydrocarbon (1·0 g.) was treated with osmium tetroxide in the usual way. The product (0·68 g.) in light petroleum (40 ml.) was adsorbed on acid-washed alumina and elution with light petroleum–benzene (4 : 1) afforded the diol which was characterised as the *di*-p-*nitrobenzoate* of 1-hydroxy*neoiso*carvomenthol which separated from methanol as cream-coloured needles, m. p. 186° (Found: C, 61·2; H, 5·5; N, 6·3%).

(*b*) *p*-Menth-1-ene (20 g.) was added to a solution of *tert.*-butyl hydroperoxide (1·1 mol.) in *tert.*-butanol (200 ml.) and a 1% solution of osmium tetroxide in *tert.*-butanol (0·5 ml.). After 4 weeks water was added and the butanol removed by distillation. The aqueous residue was extracted continuously with ether, the dried extract evaporated, and the residue distilled. The following fractions were collected: (i) b. p. 96—113°/2·5 mm. (4·6 g.), (ii) b. p. 113—123°/2·5 mm. (4·7 g.), (iii) b. p. 123—143°/2·5 mm. (3·8 g.), (iv) b. p. 143—160°/2·5 mm. (1·0 g.), (v) residue (3·5 g.). Fractions (ii) and (iii) were esterified with *p*-nitrobenzoyl chloride in pyridine, and the crude ester chromatographed in light petroleum–benzene (10 : 1; 200 c.c.) and on alumina (200 g.). This solvent eluted the *di*-p-*nitrobenzoate* of 1-hydroxycarvomenthol (880 mg.) as pale yellow prisms, m. p. 126° (after repeated fractionation from ethanol) (Found: C, 61·3; H, 5·5; N, 6·1%). Elution with light petroleum–benzene (4 : 1) yielded the di-*p*-nitrobenzoate of 1-hydroxy*neoiso*carvomenthol (1·12 g.; m. p. 186° after repeated crystallisation). Fractions (i), (iv), and (v) gave no crystalline ester. Distillation of the product from another oxidation on the same scale gave a main fraction, b. p. 102—152°/30 mm. (8·2 g.). The crude *p*-nitrobenzoates derived from this fraction were chromatographed as before. Elution with light petroleum–benzene (4 : 1) gave a mixture (1·8 g.) as needles, m. p. 165—167°, from methanol–chloroform. Ether–benzene (1 : 4) afforded the *mono*-p-*nitrobenzoate* of 1-hydroxycarvomenthol (0·5 g.) which crystallised either as pale yellow plates or clusters of needles m. p. 83°, from light petroleum (Found: C, 63·7; H, 7·1; N, 4·5%).

(*c*) *p*-Menth-1-ene (5 g.) was hydroxylated by the iodine–silver acetate method as described in Part III. The crude diol (4·5 g.), b. p. 140—154°/24 mm., was esterified with *p*-nitrobenzoyl chloride, and the ester chromatographed in light petroleum–benzene (4 : 1; 150 c.c.) on alumina (150 g.). Elution with this solvent gave the di-*p*-nitrobenzoate of 1-hydroxycarvomenthol (0·2 g.), m. p. 126° after three crystallisations from ethanol. Light petroleum–benzene (1 : 1) eluted crystals, m. p. 165—167° (1·0 g.). The mono-*p*-nitrobenzoate of 1-hydroxy*neoiso*carvomenthol (0·8 g.) was eluted with ether–benzene (1 : 4).

(*d*) 1 : 2-Epoxy-*p*-menthane mixture (12 g.) in ether (100 ml.) at 0° was saturated with hydrogen bromide and ice added. The ether extract was washed with sodium hydrogen carbonate. Distillation gave the bromohydrin mixture (14·0 g.), b. p. 78—83°/0·3 mm. Acetylation of the bromohydrin (10 g.) and treatment with silver acetate in moist acetic acid was carried out as

described for 2 : 3-epoxy-*p*-menthane.[18] The mixture of diols (4·1 g.) was separated by fractionation of the derived *p*-nitrobenzoates from alcohol, yielding the diester of 1-hydroxy*neoiso*carvomenthol (1·4 g.) and the monoester of 1-hydroxycarvomenthol (1·9 g.).

1-*Hydroxycarvomenthol*.—Hydrolysis of either the above di-*p*-nitrobenzoate, m. p. 126°, or the mono-*p*-nitrobenzoate, m. p. 83°, yielded 1-*hydroxycarvomenthol*, b. p. 88—90°/1·0 mm., needles, m. p. 49°, which could not be recrystallised (Found: C, 69·8; H, 11·6%). The *mono*-3 : 5-*dinitrobenzoate* crystallised as fine white needles, m. p. 117° from hexane (Found: C, 56·1; H, 6·1; N, 7·9%). The *monotoluene*-p-*sulphonate* crystallised as needles, m. p. 56°, from hexane (Found: C, 62·9; H, 8·3; S, 9·7. $C_{17}H_{26}O_4S$ requires C, 62·6; H, 8·0; S, 9·8%).

1-*Hydroxy*neoiso*carvomenthol*.—Hydrolysis of the di-*p*-nitrobenzoate, m. p. 186°, gave 1-*hydroxy*neoiso*carvomenthol* as needles, m. p. 72·5° after crystallisation from light petroleum (b. p. 40°) (Found: C, 69·5; H, 11·8%). Hydrolysis of the mixture, m. p. 165—167°, from methods (*b*) and (*c*) of *cis*-hydroxylation yielded needles, m. p. 70° after two crystallisations from light petroleum (b. p. 40°). The m. p. was undepressed on admixture with a sample of 1-hydroxy*neoiso*carvomenthol, m. p. 72—75°. The *mono*-p-*nitrobenzoate*, obtained from equimolar portions of the glycol and acid chloride crystallised from light petroleum as needles, m. p. 107° (Found: C, 63·4; H, 7·0; N, 4·3%).

Equilibration of p-*Menthane*-1 : 2-*diols*.—Sodium (1 g.) was added to a solution of 1-hydroxy*neo*carvomenthol (2·0 g.) in decalin (10 ml.) and the mixture boiled in oxygen-free nitrogen for 10 hr. Alcohol was added and the mixture evaporated to dryness *in vacuo* at 100°. The diol was separated by addition of water, isolation with ether, and distillation. The infrared absorption spectrum of the product in carbon disulphide was measured in the region 8—12 μ. 1-Hydroxy*iso*carvomenthol was the only diol which could be identified although about 10% of an unidentified component was present. Esterification of the glycol afforded the di-*p*-nitrobenzoate of this diol. The reaction was repeated but for periods of 16 and 24 hr., with the same result. The absorption spectra of the different samples were identical. The same result was obtained when 1-hydroxy*iso*- and 1-hydroxy*neoiso*-carvomenthol were treated similarly.

Dehydration of p-*Menthane*-1 : 2-*diols*.—The diols (0·1 g.) were heated individually with 10% sulphuric acid (1 ml.) at 100° for 2 hr. Treatment of the products with 2 : 4-dinitrophenylhydrazine sulphate solution and crystallisation of the product from methanol gave orange plates, m. p. 157°, alone or mixed with a sample of a *carvomenthone* 2 : 4-*dinitrophenylhydrazone* prepared from carvacrol by hydrogenation with W-7 Raney nickel at 100°/1000 lb. per sq. in. for 3 hr. After separation from hydrocarbon the carvomenthol mixture was oxidised with sodium dichromate–sulphuric acid, and the ketone isolated with ether. The 2 : 4-dinitrophenylhydrazone had m. p. 157° (Found: N, 16·6. $C_{16}H_{22}O_4N_4$ requires N, 16·8%).

1-*Methyl*cyclo*hexane*-cis- *and* -trans-1 : 2-*diol*.—The *trans*-diol[11] was prepared with peracetic acid as described for *p*-menth-1-ene. Esterification with *p*-nitrobenzoyl chloride and chromatography afforded the *monoester*, needles (from aqueous methanol), m. p. 103° (Found: C, 60·6; H, 6·0; N, 5·1. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%), and the *diester*, prisms (from methanol), m. p. 194° (Found: C, 59·4; H, 4·9; N, 6·4. $C_{21}H_{20}O_8N_2$ requires C, 58·9; H, 4·7; N, 6·5%). The *cis*-diol[18] was obtained in 50% yield by the iodine–silver acetate–water method. The crude diol (2·5 g.) obtained by sodium–alcohol reduction of 2-hydroxy-2-methyl*cyclo*hexanone[19] gave the *trans*-diol (1·1 g.), m. p. and mixed m. p. 84°, on crystallisation from light petroleum. Esterification of the mother-liquors gave only the di-*p*-nitrobenzoate (0·5 g.) of this diol. Samples of the *cis*- and the *trans*-diol (2·0 g.) were heated with sodium (0·8 g.) in decalin (15 ml.) for 8 and 16 hr. Alcohol was added, the mixtures were evaporated and decomposed with water, and the products were isolated with ether. The distilled products all had identical absorptions in the 8—12 μ region, corresponding to the *trans*-diol. No bands of the *cis*-isomer could be detected. Chemical separation of the products gave the *trans*-diol and its esters in all cases.

1-*Ethyl*cyclo*hexane*-cis- *and* -trans-1 : 2-*diol*.—The *trans*-diol was prepared by hydration of the epoxide with water at 110° during 5 hr. It crystallised on refrigeration for some days and formed prisms, m. p. 47°, from hexane (Found: C, 66·4; H, 11·0. $C_8H_{16}O_2$ requires C, 66·7; H, 11·1%). Esterification in pyridine at 100° during 3 hr. gave the *di*-p-*nitrobenzoate*, prisms, m. p. 222° (from benzene–light petroleum) (Found: C, 59·7; H, 4·9; N, 6·6. $C_{22}H_{22}O_8N_2$ requires C, 59·7; H, 5·0; N, 6·3%), and the *mono*-p-*nitrobenzoate*, prisms (from light petroleum) m. p. 101° (Found: C, 61·4; H, 6·3; N, 4·9. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·3; N, 4·8%).

[18] Boeseken and Mann, *Ber.*, 1923, **56**, 2409.
[19] Wilson and Read, *J.*, 1935, 1269.

The *cis*-diol was prepared in 40% yield from 1-ethyl*cyclo*hexene by the iodine–silver acetate–water method. It crystallised from light petroleum as prisms, m. p. 81° (Found: C, 67·0; H, 11·1. $C_8H_{16}O_2$ requires C, 66·7; H, 11·1%). The *di*-p-*nitrobenzoate* separated from light petroleum–chloroform as needles, m. p. 142° (Found: C, 59·9; H, 5·1; N, 6·6%). *cyclo*Hexane-1 : 2-dione (35 g.) in ether (200 ml.) was added to ethylmagnesium iodide (from 105 g. of ethyl iodide) during 2 hr. After 15 hr. at the b. p. the mixture was worked up in the usual way. *2-Ethyl-2-hydroxycyclohexanone* (17·2 g.) had b. p. 104—105°/25 mm., n_D^{25} 1·4728, d_4^{25} 1·0334 (Found: C, 68·1; H, 10·1. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). This ketol (7·5 g.) in absolute alcohol (200 ml.) was reduced with sodium (20 g.). Water was added, the alcohol distilled off, and the residue extracted with ether. Distillation gave the diol (3·5 g.) which was esterified with *p*-nitrobenzoyl chloride. Chromatography on alumina and elution with benzene gave the diester (3·0 g.), m. p. and mixed m. p. 222°, of the *trans*-glycol. Ether–benzene (1 : 10) yielded the monoester (0·7 g.), m. p. and mixed m. p. 101°. Other fractions failed to crystallise. The *cis*- and *trans*-diols, heated with sodium in decalin for 16 hr., afforded some *trans*- and some *cis*-diol: the infrared absorption spectra of both samples indicated approximately 70% of *trans*- and 30% of *cis*-diol.

1-iso*Propyl*cyclo*hexane*-cis- *and* -trans-1 : 2-*diol*.—The *cis*-isomer, obtained in 50% yield from 1-*iso*propyl*cyclo*hexene by the iodine–silver acetate–water method, separated from light petroleum as prisms, m. p. 106° (Found: C, 68·8; H, 11·6. $C_9H_{18}O_2$ requires C, 68·4; H, 11·4%). The *trans*-diol was prepared from the hydrocarbon by reaction with monoperphthalic acid and hydration of the epoxide with water at 120° during 4 hr. Crystallisation from light petroleum gave prisms, m. p. 98° (Found: C, 68·7; H, 11·8%). The *di*-p-*nitrobenzoate* had m. p. 181° (Found: C, 60·7; H, 5·2; N, 6·3. $C_{23}H_{24}O_8N_2$ requires C, 60·5; H, 5·3; N, 6·1%).

The *trans*-diol was heated with sodium and decalin as above for 8 and 16 hr. The crystalline product separated from light petroleum as prisms, m. p. 106° alone or mixed with a sample of the *cis*-diol. Similar treatment of 1-*iso*propyl*cyclo*hexane-*cis*-1 : 2-diol resulted in recovery of the starting material.

(±)cis- *and* (±)trans-*Carvotanacetol*.—The mixed 3 : 5-dinitrobenzoates derived from mercuric acetate oxidation of (±)-*p*-menth-1-ene [20] were crystallised from methanol, affording the *trans*-isomer, m. p. 94°, which was hydrolysed with potassium hydroxide in boiling ether–methanol to (±)-*trans*-carvotanacetol, b. p. 106°/17 mm., d_4^{20} 0·9290, n_D^{20} 1·4786 (Found: C, 78·2; H, 11·9. $C_{10}H_{18}O$ requires C, 77·8; H, 11·8%). A sample (0·5 g.) was hydrogenated in ethanol with W.4. Raney nickel at 100°/500 lb. per sq. in. After dilution with water the alcohol was removed and the product isolated with ether. The "*iso*carvomenthyl" 3 : 5-dinitrobenzoate [15] had m. p. 93° (Found: C, 58·8; H, 6·4. Calc. for $C_{17}H_{22}O_6N_2$: C, 58·3; H, 6·3%). The *p*-nitrobenzoate had m. p. 85° (lit.,[15] 85°).

The mother-liquors from the separation of the *trans*-ester afforded the *cis*-isomer as plates, m. p. 75° after four crystallisations from aqueous methanol (Found: C, 59·0; H, 5·7%). The ester was hydrolysed as for the *trans*-isomer and the product (0·35 g.) shaken with manganese dioxide (7 g.) in hexane (70 ml.) for 10 hr. The hexane residue afforded (±)-carvotanacetone semicarbazone, m. p. and mixed m. p. 174°. Oxidation of (±)-*trans*-carvotanacetol in the same way gave the identical result.

Dehydrations by Phosphorus Oxychloride.—1-Hydroxy*neo*carvomenthyl mono-3 : 5-dinitrobenzoate (0·04 g.) in pyridine (1·5 ml.) was treated with phosphorus oxychloride (0·15 ml.) during 24 hr. Isolation in the usual way and crystallisation from methanol gave (±)-*trans*-carvotanacetyl 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 94°. Similar treatment of the mono-*p*-nitrobenzoate afforded the (±)-*trans*-carvotanacetol derivative, as plates (from hexane), m. p. 100° (Found: C, 67·2; H, 6·8; N, 4·6. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·9; N, 4·6%). The mono-*p*-nitrobenzoate of 1-hydroxy*neoiso*carvomenthol (0·04 g.) was treated as above. Crystallisation from hexane gave the *p*-nitrobenzoate of (±)-*trans*-carvotanacetol m. p. and mixed m. p. 100°. Under the same conditions the mono-3 : 5-dinitrobenzoate of 1-hydroxycarvomenthol was recovered unchanged.

cis- *and* trans-p-*Menthane*-3 : 4-*diol*.—(±)-*p*-Menth-3-ene was prepared from 4-methyl*cyclo*hexanone by Grignard reaction with *iso*propylmagnesium bromide followed by dehydration with aqueous oxalic acid as described for (±)-*p*-menth-1-ene.[14] A cis-*diol* was obtained in 40% yield by the iodine–silver acetate–water method, described above. Esterification of the product with *p*-nitrobenzoyl chloride in the usual way, absorption on alumina, and elution with benzene gave the *mono*-p-*nitrobenzoate* which crystallised from light petroleum as prisms, m. p.

[20] Treibs and Bast, *Annalen*, 1948, **561**, 165.

138° (Found: C, 63·6; H, 7·3; N, 4·8. $C_{17}H_{23}O_5N$ requires C, 63·6; H, 7·1; N, 4·4%). Hydrolysis with methanolic potassium hydroxide, isolation with ether, and crystallisation from light petroleum gave prisms of the *diol*, m. p. 78·5° (Found: C, 70·1; H, 11·7. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%). The *mono*-3 : 5-*dinitrobenzoate* separated from light petroleum as needles, m. p. 98° (Found: C, 56·2; H, 6·2; N, 7·9. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·0; N, 7·65%). *trans*-Hydroxylation was carried out as described by Ogata [21] except that the epoxide (13·0 g.) was hydrated with water at 120° during 18 hr. The diol mixture (7·0 g.) was taken up in light petroleum (b. p. < 40°) and on refrigeration a *trans-p*-menthane-3 : 4-diol separated as prisms, m. p. 74° (73·5—76° [21]) (Found: C, 70·0; H, 11·6. Calc. for $C_{10}H_{20}O_2$: C, 69·8; H, 11·6%). The *mono*-3 : 5-*dinitrobenzoate* separated from light petroleum as needles, m. p. 156° (Found: C, 56·1; H, 5·9; N, 7·7%). The mother-liquors from the original diol crystallisation were esterified with *p*-nitrobenzoyl chloride, and the ester was washed with methanol; the precipitate (0·8 g.) when crystallised from ethanol–ethyl acetate gave a *diester* as prisms, m. p. 188° (Found: C, 61·4; H, 5·6; N, 6·0. $C_{24}H_{26}O_9N_2$ requires C, 61·3; H, 5·5; N, 6·0%). A further quantity (0·2 g.) was obtained from the mother-liquors after removal of the methanol, dissolution in light petroleum–benzene (1 : 5), and elution with this solvent. Elution with ether–benzene (1 : 5) afforded the *mono*-p-*nitrobenzoate*, m. p. 117° (Found: C, 63·9; H, 7·1; N, 4·8%), of the diol, m. p. 74°. Hydrolysis of the diester, m. p. 188°, afforded a further *diol* which separated from light petroleum as heavy prisms, m. p. 82° (Found: C, 70·0; H, 11·8%), unaffected by periodic acid at pH. 2. The infrared absorption spectrum showed the absence of a carbonyl group.

4-Bromomenthone was prepared from (±)-menthone by the method described for bromination of formyl*cyclo*hexane.[22] The hydroxy-ketone (A) was prepared by hydrolysis with aqueous potassium hydroxide.[23] Treatment with 2 : 4-dinitrophenylhydrazine sulphate gave the derivative of (±)-*p*-menth-3-en-5-one, crystallising from alcohol as red needles, m. p. 144° (Found: C, 58·0; H, 6·3. $C_{16}H_{22}O_4N_4$ requires C, 57·8; H, 6·0%) alone or mixed with a sample obtained from ketone prepared by dehydrobromination of 4-bromomenthone.[17] The same derivative was obtained when 2-hydroxymenthone [24] was converted into the 2 : 4-dinitrophenylhydrazone. The hydroxy-ketone (A) (12·0 g.) was reduced with sodium (25 g.) and alcohol (200 ml.). The bulk of the alcohol was removed, water added, and the product isolated with ether. Distillation gave a diol fraction (4·0 g.), b. p. 104—114°/2·5 mm. Esterification with *p*-nitrobenzoyl chloride, chromatography, and fractional crystallisation gave (±)-*trans*-2-hydroxymenthyl di-*p*-nitrobenzoate (2·0 g.), m. p. and mixed m. p. 117—118°, and (±)-*trans*-2-hydroxy*iso*menthyl di-*p*-nitrobenzoate [25] (0·4 g.), m. p. and mixed m. p. 164°, together with the ester of (±)-menthol (0·3 g.).

Periodate Titrations.—Rate constants at pH 10·5 were obtained as described previously.[16] Measurements in buffer pH 2 [obtained by dilution of potassium chloride (3·725 g.) in 0·100N-hydrochloric acid (106 ml.) to 1 l.] were made in the same way except that samples were quenched in a solution of potassium iodide (0·1—0·2 g.) in 0·1N-hydrochloric acid (20 ml.) and the iodine titrated with 0·01N-sodium thiosulphate.

We are grateful to Dr. A. R. H. Cole of the University of Western Australia for measurements of infrared spectra and to Professors A. K. Macbeth and G. M. Badger for their interest.

THE UNIVERSITY OF ADELAIDE. [*Received, May 15th*, 1956.]

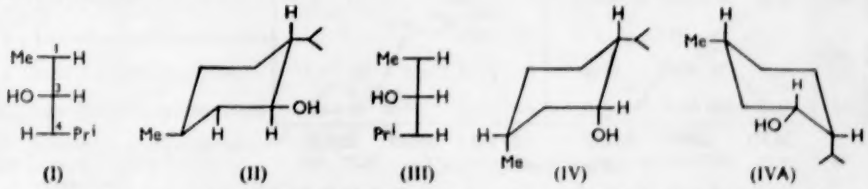
[21] Ogata, *J. Chem. Soc. Japan*, 1942, **45**, 428.
[23] Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1954, 705.
[22] Wallach, *Annalen*, 1918, **414**, 354.
[24] Jefferies, Macbeth, and Milligan, *J.*, 1954, 705.
[25] Macbeth and Robertson, *J.*, 1953, 895; 3512; 1954, 701.

843. *Stereochemistry of* cyclo*Hexane Derivatives. Part V.* Infrared Spectra and Conformations of Stereoisomeric* 1 : 2-*Diols.*

By A. R. H. Cole and P. R. Jefferies.

Infrared spectra in the hydroxyl stretching region of *p*-menthane-1 : 2-, -2 : 3-, and -3 : 4-diol and a variety of 1-alkyl*cyclo*hexane-*cis*- and -*trans*-1 : 2-diols has provided evidence on stabilities of different conformations. Distinction between secondary and tertiary free hydroxyl absorptions in the secondary-tertiary glycols has indicated hydrogen-bonding rules. Secondary hydroxyl groups form intramolecular hydrogen bonds more readily than tertiary, and axial groups more readily than equatorial. Kuhn's $\Delta\nu$ values have been obtained and interpreted in terms of conformational arguments. The structures have been assigned to two *cis*-*p*-menthane-1 : 2-diols.

It is now accepted [1-3] that at ordinary temperatures the preferred form for a monosubstituted *cyclo*hexane derivative will be the chair form in which the substituent is equatorial, and that this preference is due to repulsive forces between non-bonded atoms which will be the greater the larger is the substituent. In *trans*-1 : 2-, *cis*-1 : 3-, and *trans*-1 : 4-disubstituted *cyclo*hexanes both groups can usually adopt an equatorial position with consequent conformational stabilization,[2] whereas in the complementary *cis*-1 : 2-, *trans*-1 : 3-, and *cis*-1 : 4-isomers, which have one equatorial and one axial group, the distribution of the two conformations will depend on the relative sizes of the groups. Menthol (I) is better represented as (II), with all substituents equatorial. However, the most stable conformation of *neoiso*menthol (III) could be (IV) or (IVA) or a significant mixture of the two, since the tendency of the larger *iso*propyl group to be equatorial might be equalled or overcome by the combined effects of the hydroxyl and the methyl group. It is deduced below that *neoiso*menthol exists almost entirely as (IV), in agreement with the purely chemical evidence of Eliel.[4]



The present work is concerned with the conformations adopted by a series of 1 : 2-diols based on *cyclo*hexane and containing a range of other substituents. By using infrared absorption spectra to study intramolecular hydrogen-bonding, we have found a direct experimental method of determining the nature of these conformations at room temperature in carbon tetrachloride solution.

Kuhn [5] described infrared measurements on a series of cyclic diols with varying ring sizes, and correlated (*a*) the separation $\Delta\nu$ between the free hydroxyl stretching band (near 3630 cm.$^{-1}$) and the band due to intramolecular hydrogen bonds (near 3590 cm.$^{-1}$) with (*b*) the distance between the hydroxyl groups. In general, the closer are the two groups the more readily is the hydrogen bond formed and the larger the value of $\Delta\nu$. We have found it profitable to examine closely the intensities of the free and hydrogen-bonded hydroxyl absorption and the frequencies of the free hydroxyl groups as well as the $\Delta\nu$ values, while keeping the ring size constant.

* Part IV, preceding paper.

[1] Rasmussen, *J. Chem. Phys.*, 1943, **11**, 249; Kohlrausch and Wittek, *Z. phys. Chem.*, 1941, **48**, *B*, 177; Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149; Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1941, **63**, 2029; Beckett, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2488.

[2] Hassel, *Research*, 1950, **3**, 504.

[3] Barton, *Experientia*, 1950, **6**, 316; Barton, Hassel, Pitzer, and Prelog, *Nature*, 1953, **172**, 1096; Orloff, *Chem. Rev.*, 1954, **54**, 347.

[4] Eliel, *Experientia*, 1953, **9**, 91.

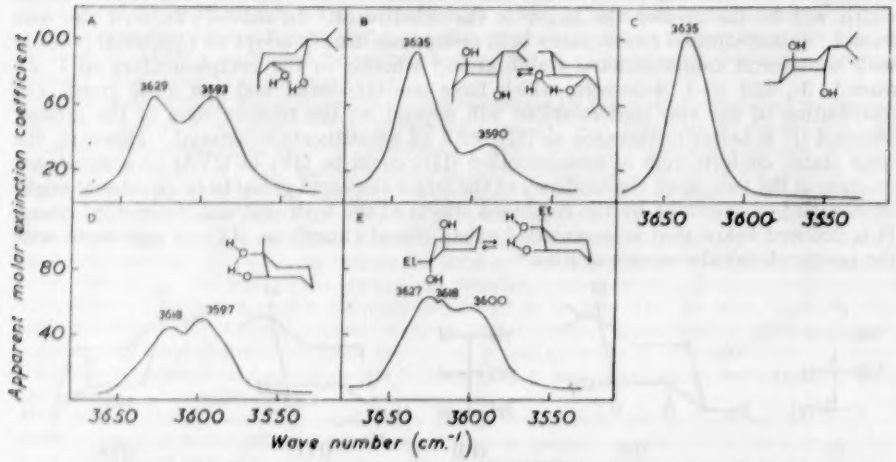
[5] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323.

Results and Discussion

The frequencies and peak intensities of the free- and bonded-hydroxyl absorption bands and the values of $\Delta\nu$ are given in the Table, with an indication of the configuration and conformation of the hydroxyl group responsible for each band.

Absorption Frequencies.—It should be noted that $\Delta\nu$ is, not the difference between the frequencies listed under Free OH and Bonded OH in the Table, but the amount by which the bonded type is lowered from its own unbonded frequency. Although Bellamy [6] doubts that they can be so distinguished, experience in this laboratory [7] shows that in carbon tetrachloride solution primary alcohols absorb near 3642 cm.$^{-1}$ ($\varepsilon \sim 70$), secondary near 3629 cm.$^{-1}$ ($\varepsilon \sim 50$—60, axial slightly higher frequency than equatorial), and tertiary near 3618 cm.$^{-1}$ ($\varepsilon \sim 45$). No primary alcohols are included in the present study, but for interpretation of the results in Table 1 it is necessary to be able to distinguish between the secondary and tertiary groups. Menthol (11) absorbs at 3628 cm.$^{-1}$, *iso*menthol at 3627

Infrared spectra in the region of hydroxyl stretching absorption.



A, cis-2-*Hydroxy*neoiso*menthol*.
B, trans-2-*Hydroxy*neoiso*menthol*.
C, trans-2-*Hydroxy*neo*menthol*.
D, 1-*Methyl*cyclo*hexane*-trans-1 : 2-*diol*.
E, 1-*Ethyl*cyclo*hexane*-trans-1 : 2-*diol*.

cm.$^{-1}$, *neo*menthol and *neoiso*menthol at 3632 cm.$^{-1}$, while guaiol [7] and a number of tertiary hydroxy-steroids [8] absorb near 3618 cm.$^{-1}$. We have therefore taken the frequencies 3629 and 3618 cm.$^{-1}$ as standard free-hydroxyl frequencies in the calculation of $\Delta\nu$ values. Now, 1-methyl*cyclo*hexane-*cis*-1 : 2-diol absorbs at 3628 cm.$^{-1}$ (free) and 3584 cm.$^{-1}$ (bonded), indicating that the secondary hydroxyl group is free and therefore the tertiary bonded. Thus the value of $\Delta\nu$ is $3618 - 3584 = 34$ cm.$^{-1}$ not $3629 - 3584 = 45$ cm.$^{-1}$ as might appear at first sight from the Table. Some of the secondary hydroxyl groups in the *p*-menthane-2 : 3-diol stereoisomers absorb slightly above 3629 cm.$^{-1}$, particularly in those compounds which form hydrogen bonds fairly readily (*e.g.*, *cis*- and *trans*-2-hydroxymenthol), and this high frequency may be related to the stability or rigidity of the cyclic bonded system. However, even with these we have used 3629 cm.$^{-1}$ as the free secondary hydroxyl frequency for the purposes of calculating $\Delta\nu$.

Relation between Spectra and Conformations.—Typical examples of the spectra are shown in the Figure and are keyed to the Table by letters. Where the conformation favours hydrogen bonding (Fig. A), the intensities of the free and the bonded absorption

[6] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 86.
[7] (*a*) Allsop, Cole, White, and Willix, (*b*) Cole and Thornton, unpublished results.
[8] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820.

are approximately equal (ε 50—60). Conformations which do not favour hydrogen bonding will thus be identified by increased intensity of the free-hydroxyl band and a decrease in that of the bonded-hydroxyl band (Figs. B and C).

Structures, hydroxyl frequencies, intensities, and band separations of 1 : 2*-diols* (*cm.*$^{-1}$, *carbon tetrachloride solutions*). *Values of* $\varepsilon_{max.}$ *are in parentheses.*

Spectral type [a]	Compound	Structure and conformation	Free OH	Free type [b]	Bonded OH	Bonded type [b]	$\Delta\nu$
A	*cyclo*Hexane-*cis*-1 ; 2-diol ...	VI; R = H	3626 (60)	e(?), s	3588 (60)	a(?)s	41
A	1-Methyl*cyclo*hexane-*cis*-1 : 2-diol	VI; R = Me	3628 (50)	e, s	3584 (52)	a, t	34
A	1-Ethyl*cyclo*hexane-*cis*-1 : 2-diol	VI; R = Et	3628 (60)	e, s	3583 (63)	a, t	35
A	1-*iso*Propyl*cyclo*hexane-*cis*-1 : 2-diol	VI; R = Pr^{i}	3629 (61)	e, s	3582 (63)	a, t	36
A	*cis*-2-Hydroxymenthol	XII; R^1 = Me, R^2 = H	3639 (58)	e(?), s	3583 (61)	a(?)s	46
A	*cis*-2-Hydroxy*iso*menthol	XII; R^1 = H, R^2 = Me	3637 (69)	e(?), s	3583 (71)	a(?)s	46
A	*cis*-2-Hydroxy*neo*menthol	XIII; R^1 = Me, R^2 = H	3633 (60)	e(?)s	3583 (62)	a(?)s	46
A	*cis*-2-Hydroxy*neoiso*menthol	XIII; R^1 = H, R^2 = Me	3629 (64)	e(?)s	3593 (64)	a(?)s	36
A	*cis*-*p*-Menthane-3 : 4-diol	XIV	3627 (61)	e, s	3581 (61)	a, t	37
A	1-Hydroxycarvomenthol (m. p. 49°)	VII	3628 (67)	e, s	3586 (58)	a, t	32
D	1-Hydroxy*neoiso*carvomenthol (m. p. 72·5°)	VIII	3618 (55)	e, t	3580 (67)	a, s	49
A	*trans-cyclo*Hexane-1 : 2-diol	VA; R = H	3631 (62)	e, s	3600 (75)	e, s	29
D	1-Methyl*cyclo*hexane-*trans*-1 : 2-diol	VA; R = Me	3618 (44)	e, t	3597 (50)	e, s	32
E	1-Ethyl*cyclo*hexane-*trans*-1 : 2-diol [c]	V, VA; R = Et	3627 } (~62) 3618 }	e, t a, s a, t	3600 (56)	e, s	29
C	1-*iso*Propyl*cyclo*hexane-*trans*-1 : 2-diol	V; R = Pr^{i}	3625 (88)	a, s; a, t	—	—	—
A	*trans*-2-Hydroxymenthol	XV; R^1 = Me, R^2 = H	3639 (46)	e, s	3590 (60)	e, s	39
A	*trans*-2-Hydroxy*iso*menthol	XV; R^1 = H, R^2 = Me	3631 (56)	e, s	3590 (65)	e, s	39
C	*trans*-2-Hydroxy*neo*menthol	XVI	3635 (100)	a, s	—	—	—
B	*trans*-2-Hydroxy*neoiso*menthol [c]	IX, IXA	3635 (93)	a, s; (e, s)	3590 (36)	e, s	39
C	*trans*-p-Menthane-3 : 4-diol	XVII	3629 (100)	a, s; a, t	—	—	—
D	1-Hydroxy*iso*carvomenthol	XVIII	3618 (52)	e, t	3597 (68)	e, s	32
C	1-Hydroxy*neo*carvomenthol	XIX	3624 (84)	a, s; a, t	—	—	—

		R^1	R^2	R^3	R^4
*iso*Menthol	X :	H	Me	OH	H
*neo*Menthol	X :	Me	H	H	OH
Carvomenthol	XI :	Me	H	H	OH
*neo*Carvomenthol	XI :	Me	H	OH	H
*iso*Carvomenthol	XI :	H	Me	H	OH
*neoiso*Carvomenthol	XI :	H	Me	OH	H

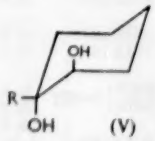
[a] See Figure. [b] e = equatorial, a = axial, s = secondary, t = tertiary. [c] Mixture of two conformations.

All the *cis*-1 : 2-diols show strong absorption due to hydrogen bonding (*e.g.*, curve A), since in all of them one hydroxyl group is equatorial and one axial and they are sufficiently close to form a hydrogen bond regardless of the conformation of the molecule. The absence of hydrogen bonding in 1-*iso*propyl*cyclo*hexane-*trans*-1 : 2-diol shows that in the competition to occupy the equatorial position the *iso*propyl group is able to overcome completely the tendency of the two hydroxyl groups plus the energy of stabilization due to the hydrogen-bond formation. The conformation of this compound must therefore be substantially (V; R = Pr^{i}). The frequency of the combined secondary and tertiary free hydroxyl groups is **3625** cm.$^{-1}$ (components not resolved), which lies between the individual frequencies given above, and the peak intensity is 88.

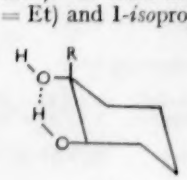
In 1-methyl*cyclo*hexane-*trans*-1 : 2-diol (Fig. D) the hydrogen bonding indicates that the two hydroxyl groups prevail over the methyl group (which is of course smaller than *iso*propyl), so that this compound exists as (VA; R = Me). The tertiary hydroxyl group is free (3618 cm.$^{-1}$) and the absence of absorption at 3629 cm.$^{-1}$ (free secondary) shows that none of the form (V; R = Me) is present. This preference of the secondary group to form the intramolecular hydrogen bond is borne out in a number of other compounds in this series (see Table) and allows us to state a first hydrogen-bonding rule, *viz.*, in *cyclo*hexane-*trans*-1 : 2-diols, where both hydroxyl groups are equatorial, a secondary group is involved in intramolecular hydrogen bonding in preference to a tertiary.

The intermediate case of 1-ethyl*cyclo*hexane-*trans*-1 : 2-diol (Fig. E) shows the presence of both conformations (V and VA; R = Et), demonstrating that they have about equal energies. The form (VA; R = Et) would be somewhat stabilized by the hydrogen-bond formation, whereas the alternative (V; R = Et) has its largest substituent group equatorial. The two free-hydroxyl bands are just resolved (3627, 3618 cm.$^{-1}$) and there is considerable hydrogen bonding. By analogy with 1-methyl*cyclo*hexane-*trans*-1 : 2-diol it might be expected that the secondary hydroxyl group would form the hydrogen bond, leaving the tertiary one free (3618 cm.$^{-1}$). The free secondary absorption (3627 cm.$^{-1}$) must be due to the diaxial form (V; R = Et).

1-Methyl*cyclo*hexane-*cis*-1 : 2-diol differs from the *trans*-compound in having its tertiary hydroxyl group bonded (free secondary 3628 cm.$^{-1}$). It must therefore be represented as (VI; R = Me). Similarly, 1-ethyl- (VI; R = Et) and 1-*iso*propyl-*cyclo*hexane-*cis*-1 : 2-

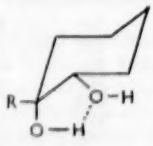


(V)

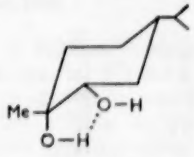


(VA)

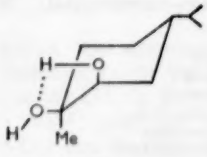
diol (VI; R = Pr^{i}) and 1-hydroxycarvomenthol (VII) all have free secondary hydroxyl (equatorial) and bonded tertiary (axial) groups. However, 1-hydroxy*neoiso*carvomenthol (VIII) has a free tertiary (3618 cm.$^{-1}$) and a bonded secondary group; here the tertiary hydroxyl group is equatorial and the secondary axial. Hence a second hydrogen-bonding rule can be stated, *viz.*, in *cyclo*hexane-*cis*-1 : 2-diols, where one hydroxyl group is equatorial and one axial, the latter is involved in intramolecular hydrogen bonding in preference to the former, regardless of whether they are secondary or tertiary.



(VI)



(VII)

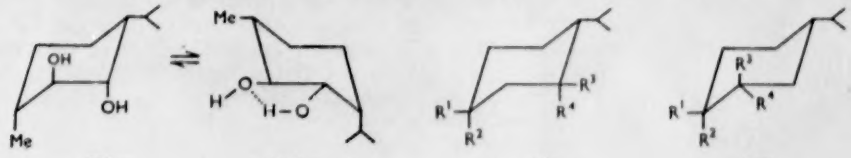


(VIII)

Bonded types deduced from this and the previous rule are shown in the Table with queries, but little doubt remains.

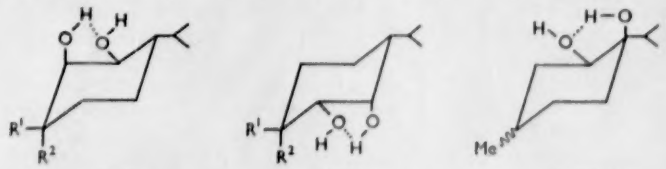
In addition to the case of 1-ethyl*cyclo*hexane-*trans*-1 : 2-diol, mixed conformations are found for *trans*-2-hydroxy*neoiso*menthol (IX, IXA) (Fig. B). Without carrying out an accurate band separation we estimate from the relative intensities of the free- and the bonded-hydroxyl absorption that the proportion of (IXA) is ~20%. Therefore, since an *iso*propyl group can hold 80% of the molecules of this compound in conformation (IX) against the combined influences of a methyl group, two hydroxyl groups, and one hydrogen bond, it may safely be deduced that *neoiso*menthol (with one less axial hydroxyl group and no hydrogen bond) is represented by (IV) rather than (IVA). The other conformations in the Table are deduced similarly. Those for the carvomenthols confirm Bose's

chemical evidence [9] (considerable doubt hitherto attended the assignment for *neoiso*-carvomenthol). For *cis-p*-menthane-3 : 4-diol the present work does not assign the configuration of the 1-methyl group. For *trans*-2-hydroxymenthol there is no proof that the 3-hydroxyl group forms the hydrogen bond but it is thus reported here since it would



(IX) (IXA) (X) (XI)

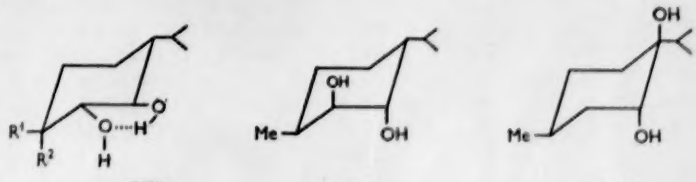
probably assume the position remote from the bulky *iso*propyl group. Although the configuration of the 1-methyl group in *trans-p*-methane-3 : 4-diol is not known, the absence of hydrogen bonding indicates that the methyl group is equatorial since if it were axial



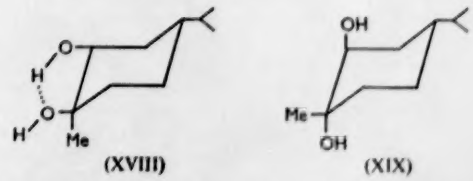
(XII) (XIII) (XIV)

both conformations would be expected (cf. *trans*-2-hydroxy*neoiso*menthol); the methyl group is thus *trans* to the *iso*propyl group. The similarity of the spectra of 1-hydroxy*iso*-carvomenthol and 1-methyl*cyclo*hexane-*trans*-1 : 2-diol provides further evidence for the structure proposed in the previous paper.

The Significance of $\Delta\nu$.—The frequency difference $\Delta\nu$ for 1-hydroxycarvomenthol and 1-hydroxy*neoiso*carvomenthol further supports the configurations. In the previous paper the difficulty associated with chemical distinction between the two *cis-p*-menthane-1 : 2-



(XV) (XVI) (XVII)

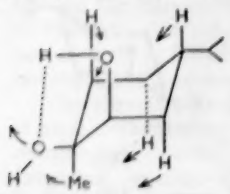


(XVIII) (XIX)

diols (m. p. 49° and 72·5° respectively) was pointed out. The most stable conformation of 1-hydroxycarvomenthol is clearly (VII). 1-Hydroxy*neoiso*carvomenthol is form (VIII) since it involves substitution of an equatorial hydroxyl group into the established most stable configuration of *neoiso*carvomenthol. The isomer, m. p. 49° ($\Delta\nu$ 32 cm.$^{-1}$), has a

[9] Bose, *Experientia*, 1952, **8**, 458.

spectrum corresponding closely to that of 1-methyl*cyclo*hexane-*cis*-1 : 2-diol (VI; R = Me) ($\Delta\nu$ 34 cm.$^{-1}$) and so must be 1-hydroxycarvomenthol (VII). The isomer, m. p. 72·5°, which shows an entirely different spectrum ($\Delta\nu$ 49 cm.$^{-1}$) is therefore 1-hydroxy*neoiso*carvomenthol (VIII). The large value of $\Delta\nu$ for the latter is required by conformation (VIII) since Kuhn [9] has shown that the magnitude of $\Delta\nu$ is inversely proportional to the ease of hydrogen-bond formation and is larger if the hydroxyl groups are close together. He attributes the fact that the value for *cyclo*hexane-*cis*-1 : 2-diol is higher than that of the *trans*-isomer to rotation of the hydroxyl groups towards each other, known to be easier for *cis*- than for *trans*-diols since in the former it is assisted by interactions (repulsions) between axial groups,[10] but opposed in the latter. The situation in (VIII) corresponds to the replacement of an axial hydrogen atom by a methyl group which causes much more rotation of the 1-hydroxyl group (cf. XX) with a corresponding increase in $\Delta\nu$. It is of interest to note that $\Delta\nu$ for the compound (VIII) is greater than that of any other studied in this investigation.



(XX)

A similar argument can be put forward on the basis of periodate oxidation rates which also depend on the distance separating the hydroxyl groups.[11] One would expect 1-hydroxy*neoiso*carvomenthol with the smaller separation of hydroxyl groups to be oxidised significantly faster than 1-hydroxycarvomenthol. The values for k_2 given in the previous paper are 8·8 and 6·5 respectively. The formation of a mono-*p*-nitrobenzoate from (VII) under conditions affording the diester of (VIII) agrees with the presence of a tertiary hydroxyl which is axial in the former and equatorial in the latter.

In 1-ethyl*cyclo*hexane-*trans*-1 : 2-diol (VA; R = Et) ($\Delta\nu$ 29 cm.$^{-1}$) the repulsion between the 1-ethyl group and the axial groups would be greater than for the 1-methyl-*trans*-compound (VA; R = Me) ($\Delta\nu$ 32 cm.$^{-1}$). In these molecules the repulsion moves the tertiary away from the secondary hydroxyl group, thereby weakening the hydrogen bonding and decreasing $\Delta\nu$. The limiting case is that of 1-*iso*propyl*cyclo*hexane-*trans*-1 : 2-diol where the repulsion is sufficient to invert the molecule and so prevent all hydrogen bonding.

A slightly different effect is responsible for the lower value of $\Delta\nu$ in *cis*-2-hydroxy*neoiso*menthol (XIII; R^1 = H, R^2 = Me) ($\Delta\nu$ 36 cm.$^{-1}$) than in the other *cis*-2-hydroxy-isomers of the menthol series for which $\Delta\nu$ = 46 cm.$^{-1}$. In *cis*-2-hydroxy*neoiso*menthol the axial 1-methyl group (R^2) will repel the hydrogen of the axial 3-hydroxyl group, orienting it away from the 2-hydroxyl group. The hydrogen bond is lengthened, and therefore weakened, relative to that in the other three compounds in which there are only axial hydrogen atoms on the same side of the molecule as the axial hydroxyl group.

Experimental

The diols used in this work were pure samples available from previous studies.[11,12]

The infrared spectra were recorded on a Grubb–Parsons single-beam spectrometer, Model S.3.A equipped with a Perkin–Elmer thermocouple, light-chopper, and No. 81 amplifier. A prism of calcium fluoride was employed and the spectral slit width at 3620 cm.$^{-1}$ was *ca.* 6 cm.$^{-1}$. By using the water-vapour absorption in the background of each spectrum as calibration, frequencies could be measured with an accuracy of ±1 cm.$^{-1}$. Measurements were made on carbon tetrachloride solutions in 3·3 and 10 mm. cells, and since the concentrations were less than 0·01M, no intermolecular hydrogen bonding was encountered. Solutions were made up by weight and molar concentrations calculated from the density. Spectral intensities, expressed as apparent molar extinction coefficient, $\varepsilon = (1/cl) \log_{10}[I_0/I]$, are estimated to be accurate to 5—10%; no corrections for finite slit width have been made, nor has band overlap been taken into account in quoting values of $\varepsilon_{max.}$ in the Table. Strictly, the integrated band area should be used as the measurement of the concentration of a particular species, but this was not

[10] Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929; Angyal and Macdonald, *J.*, 1952, 686.
[11] Jefferies, Macbeth, and Milligan, *J.*, 1954, 705.
[12] Macbeth and Robertson, *J.*, 1953, 895, 3512; 1954, 701.

considered necessary for the present purpose. The deductions of conformation depend only on relative intensities of the absorption bands due to free and bonded hydroxyl groups, and these are much more accurate than the absolute measurements.

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844. *The Decomposition of Arylazotriarylmethanes.*

By G. L. Davies, D. H. Hey, and Gareth H. Williams.

The energies and entropies of activation have been measured for the decomposition of phenylazotriphenylmethane in a number of solvents, and of a number of substituted arylazotriarylmethanes in toluene solution. Although only small differences in the rates of decomposition are shown, the activation parameters are found to exhibit much more pronounced variations, which tend to compensate one another. The mechanism of the decomposition of these and allied compounds is discussed, and explanations are suggested for the effects of solvents and substituents on the activation parameters based on a combination of the influence of resonance and solvation phenomena.

Phenylazotriphenylmethane * was first prepared by Gomberg [1] by reaction of phenylhydrazine with bromotriphenylmethane, followed by oxidation of the resulting hydrazo-compound with pentyl nitrite. It was found to decompose at its melting point (111°) with evolution of nitrogen, yielding a residue from which tetraphenylmethane could be isolated in very small yield. α-Naphthylazotriphenylmethane and some other arylazotriphenylmethanes were prepared by Gomberg and Campbell,[2] but attempts to determine the products of decomposition were unsuccessful. Wieland, Popper, and Seefried [3] allowed phenylazotriphenylmethane to decompose at 80° in ligroin in an atmosphere of nitrogen and found that triphenylmethyl radicals could be identified spectroscopically in the resulting solution. After removal of these as triphenylmethyl peroxide by passing oxygen through the solution, small amounts of triphenylmethane and tetraphenylmethane were obtained. Apart from the small amount accounted for by the formation of tetraphenylmethane, the fate of the phenyl radicals, which were assumed to be formed, remained unknown. Further experiments showed that benzene was formed, but no trace of the expected diphenyl was found. This is understandable in view of the now well-established conclusion that when phenyl radicals are formed in dilute solution the amount of dimerisation which takes place is very small. Hey [4] allowed phenylazotriphenylmethane to decompose in solution in benzene, chlorobenzene, and nitrobenzene, and showed that in benzene solution diphenyl was formed. From the decomposition in chlorobenzene, 4-chlorodiphenyl was obtained, but triphenylmethane was the only product isolated from the decomposition in nitrobenzene. In the present investigation, however, the reaction in nitrobenzene has been re-examined, and 4-nitrodiphenyl has been shown to be one of the products. The formation of these unsymmetrically substituted diaryl products was regarded as an indication that phenyl radicals were formed in the decomposition of phenylazotriphenylmethane. These conclusions were confirmed and extended by Wieland and

* The well-understood name, phenylazotriphenylmethane (and in general, arylazotriarylmethane), is used in this communication for the compound PhN:N·CPh$_3$, pending clarification of the rules governing the nomenclature of this class of compound.

[1] Gomberg, *Ber.*, 1897, **30**, 2043.
[2] Gomberg and Campbell, *J. Amer. Chem. Soc.*, 1898, **20**, 773.
[3] Wieland, Popper, and Seefried, *Ber.*, 1922, **55**, 1816.
[4] Hey, *J.*, 1934, 1966.

his co-workers,[5] who obtained 2- and 4-methyldiphenyl from the decomposition of phenylazotriphenylmethane in toluene, and 2- and 4-phenylpyridine from its decomposition in pyridine. These workers therefore put forward the following scheme for the decomposition in aromatic solvents :

$$Ph{\cdot}N{:}N{\cdot}CPh_3 \longrightarrow Ph{\cdot} + N_2 + {\cdot}CPh_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Ph{\cdot} + ArH \longrightarrow PhAr + H{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$H{\cdot} + {\cdot}CPh_3 \longrightarrow Ph_3CH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

More recent work [(Mrs.) Adams, Hey, Mamalis, and Parker [6]] has shown that 3-phenylpyridine is also formed in the reaction of phenylazotriphenylmethane with pyridine. Attention was drawn by Hey and Waters [7] to the analogy between these reactions and those of nitrosoacetanilide and of sodium benzenediazoate with the same solvents. All these reactions were considered to involve phenyl radicals as intermediates.

Further evidence for the existence of free radicals in the reactions of arylazotriarylmethanes was obtained by Hey and Misra,[8] who showed that these compounds were capable of initiating the polymerisation of styrene and methyl methacrylate, and that both aryl and triarylmethyl radicals were incorporated in the polymers. Hey, Stirling, and and Williams [9] have further confirmed this conclusion by analysis of the isomeric products of the reaction of phenylazotriphenylmethane with pyridine, and comparison of the result with those for the phenylation of pyridine under the same conditions with benzoyl peroxide, lead tetrabenzoate, phenyl iodosobenzoate, and nitrosoacetanilide.

After the inception of the work described in this communication, the kinetic aspects of the decomposition of arylazotriarylmethanes attracted the interest of several groups of workers. Huisgen and Nakaten [10] confirmed that the mechanism originally put forward by Wieland and his co-workers [5] is correct. These workers showed kinetically that no chain mechanism can be operative, and concluded from the nature of the products of the decomposition in various solvents, and in the presence of iodine, that the mechanism is not of the " kryptoradical " type similar to that advanced by Huisgen and Horeld [11] for the decomposition of aromatic diazo-acylates. Huisgen and Nakaten [10] also demonstrated the presence of hydrogen atoms in the reaction mixture by the use of the reduction indicator triphenyltetrazolium chloride. In this connection it was also observed that a small amount of aniline was formed in the decomposition in nitrobenzene. This last result has been confirmed in the present work.

The results of Cohen and Wang,[12] Alder and Leffler,[13] Leffler and Hubbard,[14] and Cohen, Leffler, and Barbato [15] will be discussed together with the results obtained in the present work in a later Section of this paper.

If Wieland's mechanism [5] involving primary dissociation into phenyl and triarylmethyl radicals and nitrogen be accepted, it is obvious that the rate of decomposition must be dependent upon the stability of the radicals produced by the primary dissociation, insofar as the stability of the transition state and hence the activation energy for the dissociation, are influenced or paralleled by this factor. Indeed, it was on the basis of this effect alone that Cohen and Wang [12] attempted to explain the variation in activation energy occasioned by the introduction of various substituents X in compounds of the type *p*-$X{\cdot}C_6H_4{\cdot}N{:}N{\cdot}CPh_3$. In order to establish the reality of such a concept, it is of interest to consider the stability of phenylazotriphenylmethane in relation to some other azo-compounds. These compounds are listed in Table 1 (cf. Wieland, vom Hove, and Börner [16]),

[5] Wieland, Heyman, Tsatsas, Juchum, Varvoglis, Labriola, Dobbelstein, and Boyd-Barrett, *Annalen*, 1934, **514**, 145.
[6] (Mrs.) Adams, Hey, Mamalis, and Parker, *J.*, 1949, 3181.
[7] Hey and Waters, *Chem. Rev.*, 1937, **21**, 184.
[8] Hey and Misra, *J.*, 1949, 1807.
[9] Hey, Stirling, and Williams, *J.*, 1955, 3963.
[10] Huisgen and Nakaten, *Annalen*, 1954, **586**, 70.
[11] Huisgen and Horeld, *ibid.*, 1949, **562**, 137.
[12] Cohen and Wang, *J. Amer. Chem. Soc.*, 1953, **75**, 5504.
[13] Alder and Leffler, *ibid.*, 1954, **76**, 1425.
[14] Leffler and Hubbard, *J. Org. Chem.*, 1954, **19**, 1089.
[15] Cohen, Leffler, and Barbato, *J. Amer. Chem. Soc.*, 1954, **76**, 4169.
[16] Wieland, vom Hove, and Börner, *Annalen*, 1926, **446**, 31.

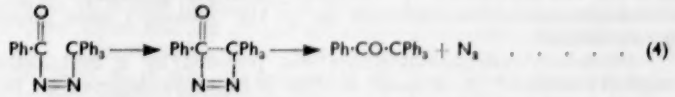
in order of increasing stability. The decomposition of benzoylazotriphenylmethane was studied by Wieland, vom Hove, and Börner,[16] and that of other acylazotriphenylmethanes by Wieland, Hintermaier, and Dennstedt,[18] and Wieland and his co-workers.[5] It was shown that benzoylazotriphenylmethane decomposes in xylene solution much more readily

TABLE 1.

Compound	Stability	Compound	Stability
Azotriphenylmethane $Ph_3C{\cdot}N{:}N{\cdot}CPh_3$	Does not exist	Azodibenzoyl * $Ph{\cdot}CO{\cdot}N{:}N{\cdot}COPh$	Incomplete decomp. at 135°
Benzylazotriphenylmethane $Ph_3C{\cdot}N{:}N{\cdot}CH_2Ph$	Does not exist	Benzoylazobenzene $Ph{\cdot}CO{\cdot}N{:}NPh$	Stable at 135°
Benzoylazotriphenylmethane $Ph_3C{\cdot}N{:}N{\cdot}COPh$	Decomp. at room temp.	Azobenzene $Ph{\cdot}N{:}NPh$	Very stable (b. p. 293° without decomp.)
Phenylazotriphenylmethane $Ph_3C{\cdot}N{:}NPh$	Decomp. at 70—80°		

* Leffler and Bond,[17] recently showed that azodibenzoyl decomposes slowly at 110° in benzene solution to give a complex mixture.

than phenylazotriphenylmethane: nitrogen is evolved, and benzoyltriphenylmethane is obtained in up to 70% yield. It was suggested that in contrast to phenylazotriphenylmethane, where only about 5% of tetraphenylmethane is formed, and which was therefore considered to proceed by the mechanism involving phenyl and triphenylmethyl radicals, benzoylazotriphenylmethane decomposed by an intramolecular mechanism (4), which does not involve free-radical intermediates. In support of this scheme, the stability of azodibenzoyl was cited as evidence of the relative strength of the Ph·CO–N bond when



(4)

compared with that of the Ph_3C–N bond. A re-interpretation of these results is, however, now possible in the light of more modern ideas concerning the relative stability of radicals. The benzoyl radical, by virtue of the contribution of canonical forms such as (I) and (II) to the resonance hybrid, would be expected to be a more stable, and consequently less reactive radical, than phenyl.

(I) (II)

This decrease in reactivity might well reduce considerably, or even eliminate, the ability of benzoyl radicals to react with an aromatic solvent. In such circumstances the life of a benzoyl radical in solution must be sufficiently prolonged to allow fruitful collisions with triphenylmethyl radicals, yielding benzoyltriphenylmethane. Thus the production of benzoyltriphenylmethane, and the relative stability of benzoylazotriphenylmethane when compared with phenylazotriphenylmethane, are not inconsistent with a mechanism involving primary dissociation into free radicals, in view of the expected non-reactivity of the benzoyl radical. This interpretation is supported by the observation of Wieland, Hintermaier, and Dennstedt [18] that benzylazotriphenylmethane is unstable, all attempts to prepare it leading to *asym.*-tetraphenylethane. This would be expected from the above considerations, in view of the resonance-stabilisation of the benzyl radical, whose low reactivity is well known. It has also been shown by Wieland, Ploetz, and Indest [19] that in the decomposition of benzoylazotriphenylmethane, the yield of nitrogen is not quantitative, and that a small amount of benzoylhydrazine is formed. This cannot be accommodated on the basis of an intramolecular mechanism, but is consistent with the postulate of a primary dissociation into free radicals, provided that it is assumed that the

[17] Leffler and Bond, *J. Amer. Chem. Soc.*, 1956, **78**, 335.
[18] Wieland, Hintermaier, and Dennstedt, *Annalen*, 1927, **452**, 1.
[19] Wieland, Ploetz, and Indest, *ibid.*, 1937, **532**, 166.

two bonds are not broken simultaneously, but that the initial stage is the production of triphenylmethyl and benzoylazo-radicals, some of which subsequently lose nitrogen (5 and 6):

$$Ph\cdot CO\cdot N{:}N\cdot CPh_3 \longrightarrow Ph\cdot CO\cdot N{:}N\cdot + \cdot CPh_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$Ph\cdot CO\cdot N{:}N\cdot \longrightarrow Ph\cdot CO\cdot + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Thus it appears that Wieland's mechanism involving primary dissociation is consistent with the known facts concerning the decomposition of azo-compounds of this type. The present investigation was carried out with the object of confirming this postulate as applied to arylazotriarylmethanes and of discovering what other factors, if any, contribute to the stability of compounds of this type.

Experimental

Materials.—Arylazotriarylmethanes were prepared by the general method employed by Gomberg and Campbell,[3] Gomberg and Berger,[20] and Wieland, Popper, and Seefried,[3] in which an arylhydrazine (2 mols.) is treated with the appropriate triarylchloromethane (1 mol.) in ether. Oxidation of the resulting arylhydrazotriarylmethane was carried out by the method of Wieland, vom Hove, and Börner,[16] using alkaline potassium ferricyanide, except that for *m*- and *p*-nitrophenylazotriphenylmethane pentyl nitrite was used (Gomberg and Campbell [3]).

Phenylazotriphenylmethane crystallised from benzene–ethanol in yellow needles, m. p. 111° (decomp.). *p*-Tolylazotriphenylmethane, m. p. 103·5° (decomp.) (15·9 g.), was obtained from triphenylchloromethane (27·8 g.) and *p*-tolylhydrazine (24·4 g.), which was prepared from *p*-toluidine by Macpherson and Stratton's method [21] (Gomberg and Campbell [3] reported m. p. 103·5° for this compound). *p*-Chlorophenylazotriphenylmethane, m. p. 108° (decomp.), and *p*-bromophenylazotriphenylmethane, m. p. 112° (decomp.), were prepared as described by Hey and Misra.[8]

p-Nitrophenylazotriphenylmethane was prepared by a modification of Gomberg and Campbell's method.[3] A saturated solution of triphenylchloromethane (9·0 g.) in ethyl acetate was added to a boiling solution of *p*-nitrophenylhydrazine (10·2 g.) in ethyl acetate (150 ml.). The mixture was boiled under reflux for 20 min., during which the brownish-yellow *p*-nitrophenylhydrazine hydrochloride was precipitated. After cooling, the mixture was filtered and most of the ethyl acetate distilled off. Ethanol was added to the residue after cooling, to precipitate the *p*-nitrophenylhydrazotriphenylmethane (10 g.; m. p. 170°). This product (10 g.) was suspended in ether (250 ml.) and an excess of pentyl nitrite was added together with a drop of acetyl chloride to start the reaction. The suspension was boiled under reflux for 5—10 min. The ether was allowed to evaporate at room temperature, orange crystals of *p*-nitrophenylazotriphenylmethane being deposited. The product had m. p. 120° (decomp.) (9·29 g.) after purification by precipitation from benzene by ethanol. Gomberg and Campbell [3] reported m. p. 118·5° (decomp.).

m-Tolylhydrazine was prepared by the method used by Macpherson and Stratton [21] for *p*-tolylhydrazine. The quantities of reagents and experimental details are identical with those described for the latter compound, except that, on neutralisation of the hydrochloride, *m*-tolylhydrazine separated as an oil. This was extracted with ether, and the crude product obtained from the dried extract after removal of the ether was distilled under vacuum, yielding *m*-tolylhydrazine (b. p. 132—134°/16 mm.; 243°/760 mm.), in 76·5% yield. Buckha and Schachtabeck [22] reported b. p. 240—244° for this compound. *m*-Tolylhydrazine (12·2 g.) was allowed to react in ethereal solution with triphenylchloromethane (13·9 g.), by use of the procedure already described except that in this case heating was maintained for 5 hr. The resulting hydrazo-compound was oxidised with potassium ferricyanide (80 g.) in water (300 ml.) and 2N-sodium hydroxide (100 ml.). After being ground with a little ethanol and collected, the product was dissolved in the minimum quantity of benzene, and precipitated by the addition of an equal volume of ethanol. This procedure was repeated four times, to give *m-tolylazotriphenylmethane* (10·5 g.), m. p. 101·5° (decomp.) (Found: C, 85·8; H, 6·3. $C_{26}H_{22}N_2$ requires C, 86·2; H, 6·1%).

m-Chlorophenylazotriphenylmethane, m. p. 107° (decomp.) (11·0 g.), was prepared from

[20] Gomberg and Berger, *Ber.*, 1903, **36**, 1088.
[21] Macpherson and Stratton, *J. Amer. Chem. Soc.*, 1915, **37**, 908.
[22] Buckha and Schachtabeck, *Ber.*, 1889, **22**, 841.

m-chlorophenylhydrazine (b. p. 160—164°/21 mm.; 14·25 g.) and triphenylchloromethane (13·9 g.); Gomberg and Campbell [2] reported m. p. 109°. *m*-Nitrophenylazotriphenylmethane, m. p. 111° (decomp.) (14 g.), was prepared from *m*-nitrophenylhydrazine (m. p. 93°; 15·3 g.), obtained in 52% yield by Bischler and Brodsky's method,[23] and triphenylchloromethane (13·9 g.) by the method used for the preparation of the *para*-isomeride; Gomberg and Campbell [2] reported m. p. 111—112° (decomp.).

Tri-*p*-tolylmethanol was prepared by Mothwurf's procedure,[24] but from methyl *p*-toluate (20 g.) and *p*-bromotoluene (51·3 g.). The product was subjected to steam-distillation to remove volatile impurities and to the residual thick oil dissolved in a small amount of benzene was added light petroleum (b. p. 60—80°). This solution was passed through a short alumina column, which was eluted with light petroleum (b. p. 60—80°). The combined eluate was evaporated to small bulk and allowed to cool; tri-*p*-tolylmethanol crystallised in white plates, m. p. 97° (14 g.). Mothwurf [24] reported m. p. 96·5°. This alcohol (14 g.) was boiled with acetyl chloride (100 ml.) for 15 min. After removal of the excess of acetyl chloride by distillation the residual chlorotri-*p*-tolylmethane was recrystallised from light petroleum (yield, 12·5 g.; m. p. 180°); Mothwurf [24] reported m. p. 181°. Phenylazotri-*p*-tolylmethane, m. p. 113° (decomp.) (7·3 g.), was prepared by the general method described, from phenylhydrazine (6·5 g.) and chlorotri-*p*-tolylmethane (9·6 g.); Mothwurf [24] reported m. p. 113—116° (decomp.).

Tri-*p*-chlorophenylmethanol was prepared by Baeyer's method [25] from *p*-chloroiodobenzene (47·6 g.) (prepared by the iodination of chlorobenzene by Datta and Chatterjee's method [26]), magnesium (4·9 g.), and methyl *p*-chlorobenzoate (15 g.). Purification of the product by the method described for tri-*p*-tolylmethanol gave tri-*p*-chlorophenylmethanol (11 g.) in colourless hexagonal plates, m. p. 97°: Baeyer [25] reported m. p. 98—98°. Chlorotri-*p*-chlorophenylmethane, m. p. 112—113°, was prepared in 80% yield from tri-*p*-chlorophenylmethanol by the method described for chlorotri-*p*-tolylmethane; Baeyer [25] reported m. p. 113°. *Phenylazotri*-p-*chlorophenylmethane*, m. p. 110° (decomp.) (5·2 g.), was prepared by the general method described above, from phenylhydrazine (4·3 g.) and chlorotri-*p*-chlorophenylmethane (7·6 g.) (Found: C, 66·5; H, 4·1. $C_{31}H_{17}N_2Cl_3$ requires C, 66·4; H, 3·9%).

Tri-*p*-bromophenylmethanol, m. p. 131°, was prepared in 29% yield by the method described for the preparation of tri-*p*-chlorophenylmethanol; Gomberg and Cone [27] reported m. p. 131°. Tri-*p*-bromophenylchloromethane, m. p. 152°, was obtained in 93% yield from tri-*p*-bromophenylmethanol and acetyl chloride in the manner described for the preparation of chlorotri-*p*-chlorophenylmethane; Gomberg and Cone [27] reported 153°.

Phenylazotri-*p*-bromophenylmethane could not be prepared. Tri-*p*-bromophenylchloromethane was condensed with phenylhydrazine by the general method already described. On oxidation of the resulting ethereal solution of *N*-tri-*p*-bromophenylmethyl-*N'*-phenylhydrazine with alkaline potassium ferricyanide, considerable frothing was observed, and a brown tar was obtained from which no azo-compound could be isolated. To a portion of this tar (3 g.) a small amount of ethanol was added. Scratching with a glass rod caused the tar to solidify, and after it had been allowed to stand for ½ hr. the solid was filtered off, dissolved in benzene, and passed through an alumina column, which was subsequently eluted with 1 : 1 benzene–light petroleum (b. p. 60—80°; 300 ml.). Evaporation of the eluate yielded ethyl tri-*p*-bromophenylmethyl ether (1·3 g.), which was obtained in clusters of colourless prisms, m. p. 206°, alone or mixed with a specimen prepared by Gomberg and Cone's method.[27] Further elution of the column with ethanol (100 ml.) yielded an unidentified substance (0·25 g.), m. p. 172° (Found: C, 46·9; H, 1·9%).

Tri-*p*-nitrophenylmethane [28] (20 g.) was oxidised with chromium trioxide in glacial acetic acid by Fischer and Fischer's method.[29] Recrystallisation of the product from benzene gave tri-*p*-nitrophenylmethanol (9·6 g.), m. p. 191°; Fischer and Fischer [29] reported m. p. 172°, and Montagne [28] reported m. p. 193°. Chlorotri-*p*-nitrophenylmethane was prepared from tri-*p*-nitrophenylmethanol (4·1 g.) by Gomberg's method.[30] Purification of the product by chromatography on alumina, and recrystallisation from benzene, yielded pale orange crystals of *chlorotri*-p-*nitrophenylmethane* (3 g.), m. p. 209° (Found: C, 55·0; H, 2·9. $C_{19}H_{12}O_6N_3Cl$

[23] Bischler and Brodsky, *Ber.*, 1889, **22**, 2809.
[24] Mothwurf, *Ber.*, 1904, **37**, 3153.
[25] Baeyer, *Ber.*, 1905, **38**, 586.
[26] Datta and Chatterjee, *J. Amer. Chem. Soc.*, 1919, **41**, 293.
[27] Gomberg and Cone, *Ber.*, 1906, **39**, 3284.
[28] Montagne, *Rec. Trav. chim.*, 1905, **24**, 125.
[29] Fischer and Fischer, *Annalen*, 1878, **194**, 256.
[30] Gomberg, *Ber.*, 1904, **37**, 1640.

requires C, 55·1; H, 2·9%). Gomberg [30] failed to purify this compound, and did not record its m. p.

Phenylazotri-*p*-nitrophenylmethane could not be obtained. Phenylhydrazine (1·7 g.) and chlorotri-*p*-nitrophenylmethane (3·6 g.) were boiled under reflux in ether for 24 hr. Oxidation of the resulting solution, after filtration, with alkaline potassium ferricyanide gave only a red tar.

Purification of Solvents.—Toluene was boiled under reflux with 1% sodium amalgam for 8 hr. and after filtration was distilled through a 4-ft. helix-packed column. Nitromethane was boiled under reflux in a stream of air for 5 hr. to remove volatile impurities : it was then boiled under reflux for 4 hr. with charcoal, filtered, and fractionally distilled. Acetic acid was boiled for 10 hr. with chromium trioxide and fractionally distilled, the fraction boiling at 118° being collected : it was then fractionally frozen to constant m. p. 16·3°. Nitrobenzene was fractionally frozen several times, dried (P_2O_5), and fractionally distilled (b. p. 109°/26 mm.). *n*-Propyl alcohol was shaken with solid sodium hydroxide, filtered, and distilled : after being dried (CaO), it was fractionally distilled.

Kinetic Measurements.—The apparatus was so designed that, after the introduction of the azo-compound and the solvent into the reaction vessel, the apparatus could be swept free of air with nitrogen, and the reaction started without opening any part of it to the atmosphere. The reaction flasks were of approx. 30 ml. capacity. Each flask carried a side-arm which could be closed by a tap and was used for the introduction of nitrogen. The upper section of each reaction vessel, which was attached to the lower by means of a B24 joint, carried a stirrer, and a side-arm, which was connected to a nitrometer. The stirrers rotated in tightly fitting polyvinyl chloride glands, which were lubricated with a mixture of Vaseline and liquid paraffin. These glands were found to be completely airtight for pressure differences up to 30 cm. of water—a value which was about 6 times the maximum encountered during a run. The nitrometers were of 50 ml. capacity and could be read to the nearest 0·05 ml. The closed limb of each was fitted with a three-way tap, by means of which the reaction vessel could be connected either to the atmosphere or to the nitrometer. The nitrometers contained water saturated with nitrogen. The reaction flasks were immersed in an oil-filled thermostat, which was accurate to $\pm 0{\cdot}05°$.

Kinetic experiments were conducted as follows. All solvents were saturated with dry nitrogen immediately before use. A weighed portion of the azo-compound was introduced into the reaction vessel in a sealed, thin-walled glass ampoule, which was allowed to float on the solvent. The apparatus was then assembled and the reaction vessel connected to the atmosphere by means of the three-way tap, the closed limb of the nitrometer being full of water. The stirrer was raised above the surface of the solvent and nitrogen was passed through the apparatus for 1 hr. At the end of this time the apparatus was closed to the nitrogen supply, and connected to the nitrometer by the three-way tap. The reaction vessel was lowered into the thermostat and allowed to attain thermal equilibrium. The initial nitrometer reading was taken, and the reaction started by depressing the stirrer to break the glass ampoule. This movement of the stirrer created an error in the initial nitrometer reading, and a correction for this was applied at the end of the run by returning the stirrer to its original position and noting the difference in volume as registered on the nitrometer. This difference was then added to the observed initial reading. Rapid stirring was maintained throughout the reaction. Nitrometer readings were taken at regular intervals, depending on the rate of the particular reaction being observed. The " infinity " reading was taken after an interval of time equal to at least 10 times the half-life of the reaction. A further reading was taken after a few hours to ensure that no change due to leakage or any other cause had taken place. The atmospheric pressure and temperature were found normally to remain sufficiently constant during a run, but were often found to have changed when the time came to take the " infinity " reading. It was usually possible, by means of heaters or fans, to bring the room temperature back to its original value, although a few runs had to be repeated when the difference was too great. The pressure correction was made by raising or lowering the open limb of the nitrometer by the requisite amount. Since all the reactions studied were kinetically of the first order, it was unnecessary to correct individual readings to S.T.P. Velocity constants were calculated from the observed readings according to the first-order law, which, in all cases, was strictly obeyed. All measurements were carried out in duplicate or triplicate.

Kinetic Results.—In order to establish the first-order law for the reaction, phenylazotriphenylmethane was allowed to decompose in toluene solution at various concentrations. The results, which are given in Table 2, show that the measured first-order velocity constant k_1 is independent of the initial concentration. This result is in accord with the findings by Cohen and

Wang,[18] and is indicative of a unimolecular reaction. All subsequent decompositions were carried out at concentrations within the range shown in Table 2, except that of phenylazotriphenylmethane in *n*-propyl alcohol, where the low solubility demanded a lower concentration (~0·014M).

First-order velocity constants for the decomposition at various temperatures of phenylazotriphenylmethane in various solvents, of *para*- and *meta*-substituted arylazotriphenylmethanes in toluene, and of various phenylazotriarylmethanes in toluene are given in Tables 3—6.

TABLE 2. *Decomposition of phenylazotriphenylmethane in toluene at 60·35°.*

Initial concn. (M)	10^4k_1 (sec.$^{-1}$)	10^4k_1 (mean) (sec.$^{-1}$)
0·035	6·33, 6·29	6·31
0·055	6·33, 6·38	6·35
0·075	6·33, 6·33	6·33

TABLE 3. *Decomposition of phenylazotriphenylmethane in various solvents.*

Solvent	Temp.	10^4k_1 (mean) (sec.$^{-1}$)	Solvent	Temp.	10^4k_1 (mean) (sec.$^{-1}$)
Toluene	49·55°	1·61	Acetic acid	54·65°	2·90
	54·65	3·00		60·35	5·57
	60·35	6·33		65·15	10·2
	65·15	11·2			
Nitromethane	54·65	2·40	*n*-Propyl alcohol	54·65	2·53
	60·35	5·18		60·35	6·00
	65·15	9·36		65·15	11·2
Nitrobenzene	54·65	2·37			
	60·35	4·80			
	65·15	8·49			

TABLE 4. *Decomposition of p-*$X{\cdot}C_6H_4{\cdot}N{:}N{\cdot}CPh_3$ *in toluene.*

X	Temp.	10^4k_1 (mean) (sec.$^{-1}$)	X	Temp.	10^4k_1 (mean) (sec.$^{-1}$)
Me	49·55°	1·75	Br	54·65°	1·30
	54·65	3·14		60·35	2·63
	60·35	5·98		65·15	4·99
	65·15	11·3		70·30	8·98
Cl	54·65	1·41	NO_2	60·35	1·40
	60·35	3·09		65·15	2·61
	65·15	5·50		70·30	4·87
	70·30	9·67		74·85	8·75

TABLE 5. *Decomposition of m-*$X{\cdot}C_6H_4{\cdot}N{:}N{\cdot}CPh_3$ *in toluene.*

X	Temp.	10^4k_1 (mean) (sec.$^{-1}$)	X	Temp.	10^4k_1 (mean) (sec.$^{-1}$)	X	Temp.	10^4k_1 (mean) (sec.$^{-1}$)
Me	49·55°	1·55	Cl	54·65°	1·27	NO_2	60·35°	1·35
	54·65	3·22		60·35	2·68		65·15	2·62
	60·35	6·81		65·15	5·45		70·30	5·22
	65·15	12·8		70·30	10·3		74·85	9·25

TABLE 6. *Decomposition of* $Ph{\cdot}N{:}N{\cdot}C(C_6H_4X\text{-}p)_3$ *in toluene.*

X	Me				Cl			
Temp.	44·75°	49·55°	54·65°	60·35°	44·75°	49·55°	54·65°	60·35°
10^4k_1 (mean) (sec.$^{-1}$)	0·776	1·62	2·98	6·21	2·34	4·80	8·72	16·7

The compounds with X = Br or NO_2 decompose under conditions of preparation.

Decomposition of Phenylazotriphenylmethane in Toluene in the Presence of Iodine.—This experiment was carried out in order to ascertain whether the rate of decomposition was affected by the nature of the subsequent reactions of the free radicals. Owing to the reversibility of the reaction of triphenylmethane with iodine (cf. Waters [31]), the reaction was carried out in the presence of ethanol and pyridine according to the method used by Ziegler, Ewald, and Orth [32] for the measurement of the rate of decomposition of hexaphenylethane. The ethanol and

[31] Waters, "The Chemistry of Free Radicals," Oxford Univ. Press, 1950, p. 44.
[32] Ziegler, Ewald, and Orth, *Annalen*, 1930, **479**, 277.

pyridine serve to repress the reverse reaction by reacting with iodotriphenylmethane to form the stable, colourless products, ethyl triphenylmethyl ether and pyridine hydriodide (7 and 8):

$$Ph_3CI + HOEt \longrightarrow Ph_3C{\cdot}OEt + HI \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$HI + C_5H_5N \longrightarrow C_5H_5N,HI \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

A mixture of iodine (1·46 g.), ethanol (2 ml.) and pyridine (4 ml.) was made up to 100 ml. with toluene. A portion (25 ml.) of this solution was transferred to a reaction flask, and the rate of decomposition of phenylazotriphenylmethane determined in the usual way at 60·35°. At the end of the reaction, the solution was titrated against standard sodium thiosulphate. A further portion (25 ml.) of the original solution was similarly titrated, the difference in the two titrations being a measure of the amount of iodine consumed in reaction with the free radicals. The velocity constant for the decomposition was found to be unaltered by the presence of the added substances, and the amount of iodine taken up in the reaction was equal to 90% of that required for reaction with all the phenyl and triphenylmethyl radicals produced. This result confirms unequivocally the conclusion that the fate of the radicals produced is not kinetically significant and that, therefore, the production of the radicals is the rate-determining stage. A similar conclusion has been reached by Huisgen and Nakaten.[10]

Decomposition of Phenylazotriphenylmethane in Nitrobenzene.—Acid-extraction of the crude product of the reaction of phenylazotriphenylmethane (10 g.) with nitrobenzene (350 ml.) at 80° revealed the presence of aniline (0·1 g.). The acid-washed product was chromatographed on alumina, and the following products were obtained, which were identified by mixed m. p.: triphenylmethane (1·98 g.), m. p. 92°; triphenylmethanol (0·51 g.), m. p. 162°; 4-nitrodiphenyl (0·64 g.), m. p. 114°. A similar reaction, carried out with the passage of a current of dry oxygen, gave no triphenylmethane but triphenylmethyl peroxide (0·46 g.), m. p. 185°, triphenylmethanol (2·50 g.), m. p. 162°, and 4-nitrodiphenyl (0·46 g.), m. p. 114°.

Discussion

Activation Parameters.—Values of the energy of activation, E, the non-exponential factor B, and the entropy of activation ΔS^*, for the various reactions studied are given in Tables 7—10. In general, when the same quantity has been measured by previous workers,[12,14] the agreement between the results is good.

Table 7. *Decomposition of phenylazotriphenylmethane in various solvents.*

Solvent	E (kcal. mole^{-1})	B	ΔS^* (cal. deg.$^{-1}$)
Toluene	27·4 ± 0·6	5·3 × 10^{14}	8 ± 2
Nitromethane	28 ± 1	1·1 × 10^{15}	10 ± 3
Nitrobenzene	27 ± 1	2·2 × 10^{14}	7 ± 3
Acetic acid ...	27 ± 1	2·7 × 10^{14}	7 ± 3
n-Propyl alcohol ...	31 ± 2	1·1 × 10^{17}	19 ± 6

Table 8. *Decomposition of* p-X·C_6H_4·N:N·CPh_3 *in toluene.*

X	E (kcal. mole^{-1})	B	ΔS^* (cal. deg.$^{-1}$)
Me	25·2 ± 0·6	1·95 × 10^{13}	2 ± 2
Cl	27·3 ± 0·6	2·2 × 10^{14}	7 ± 2
Br	27·8 ± 0·6	4·2 × 10^{14}	8 ± 2
NO_2	29·3 ± 0·6	2·1 × 10^{15}	11 ± 2

Table 9. *Decomposition of* m-X·C_6H_4·N:N·CPh_3 *in toluene.*

X	E (kcal. mole^{-1})	B	ΔS^* (cal. deg.$^{-1}$)
Me	29·2 ± 0·6	8·7 × 10^{15}	14 ± 2
Cl	29·8 ± 0·6	8·8 × 10^{15}	14 ± 2
NO_2	30·5 ± 0·6	1·23 × 10^{16}	15 ± 2

Table 10. *Decomposition of* Ph·N:N·$C(C_6H_4X$-$p)_3$ *in toluene.*

X	E (kcal. mole^{-1})	B	ΔS^* (cal. deg.$^{-1}$)
Me	27·5 ± 0·6	6·3 × 10^{14}	9 ± 2
Cl	26·0 ± 0·6	1·7 × 10^{14}	6 ± 2

Mechanism of the Decomposition.—The results presented in Table 2, and those of Cohen and Wang,[12] indicate that the rate of decomposition is independent of the initial concentration of phenylazotriphenylmethane, and that the first-order kinetic law is strictly obeyed. Huisgen and Nakaten,[10] by their discovery that neither chain-inhibitors nor chain-initiators affect the reaction, have demonstrated that no chain reaction is involved. It is therefore apparent that the reaction is kinetically of the first-order and is unimolecular. The results of the decomposition of phenylazotriphenylmethane in the presence of iodine

show that the kinetics are unaffected by the nature of the subsequent reactions undergone by the free radicals, and so the rate of the reaction must be determined by homolytic dissociation into free radicals and nitrogen. The products of the decomposition in aromatic solvents indicate that under these conditions the aryl radicals react with the solvent by substitution, and the hydrogen atoms so formed react subsequently with any reducible species which may be present. Triphenylmethyl radicals fall into this category, and hence triphenylmethane is a major product. This does not, however, eliminate the possibility that reduction products of the other species present may not be formed; thus, for example, a little aniline is formed from the decompositon in nitrobenzene. Such products, however, would be expected only in small amount, since the highly reactive triphenylmethyl radicals may be present at appreciable concentrations.

It is of interest to examine the order of bond-fission in the decomposition. It is possible that both bonds may be broken simultaneously in a single rate-determining stage, or that they are broken successively in a two-stage process, of which one stage is rate-determining. Wieland, vom Hove, and Börner,[16] and Wieland, Hintermaier, and Dennstedt,[18] have shown that benzoylazotriphenylmethane decomposes more readily than phenylazotriphenylmethane, producing up to 70% of benzoyltriphenylmethane together with some *p*-benzoyltriphenylmethyl. Wieland, Ploetz, and Indest [19] have shown that a small amount of benzoylhydrazine is also produced in this reaction, and that the yield of nitrogen is not quantitative. The mechanism of this reaction was discussed earlier in this paper, and in the light of that discussion, it is difficult to imagine any route whereby benzoylhydrazine might be formed, other than the reduction of benzoylazo-radicals ($Ph{\cdot}CO{\cdot}N{:}N{\cdot}$) by hydrogen atoms resulting from the reaction of benzoyl radicals with triphenylmethyl, yielding *p*-benzoyltriphenylmethyl and hydrogen. It is apparent, therefore, that the decomposition of benzoylazotriphenylmethane is a two-stage process, and that the nitrogen–triphenylmethyl bond is the first to break, producing the radicals $Ph{\cdot}CO{\cdot}N{:}N{\cdot}$ and $\cdot CPh_3$. The former radicals must be assumed to be sufficiently stable to permit the reduction of a few radicals before decomposition. An examination of the relative stability of azobenzene, benzoylazobenzene, and azodibenzoyl (Table 1) reveals that the ease of decomposition increases in that order, and indicates that the bond Ph–N is stronger than Ph·CO–N. When considered in conjunction with the above conception of the decomposition of benzoylazotriphenylmethane, this fact suggests that the decomposition of arylazotriarylmethanes proceeds along an analogous route [eqns. (9) and (10)]:

$$Ph{\cdot}N{:}N{\cdot}CPh_3 \longrightarrow Ph{\cdot}N{:}N{\cdot} + \cdot CPh_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$Ph{\cdot}N{:}N{\cdot} \longrightarrow Ph{\cdot} + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

Nitrogen evolution in this reaction is, however, quantitative, and no products derived from the phenylazo-radical ($Ph{\cdot}N{:}N{\cdot}$) have been isolated. This is an indication that the second stage of the above scheme is very rapid, and hence it is the first stage which must be rate-determining. Such a view of the reaction is consistent with the effects of substituents in the phenyl group of phenylazotriphenylmethane, and this consistency lends additional support to the view of the reaction which has been developed.

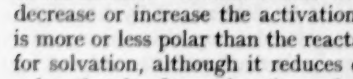
Solvent Effects.—The most striking feature of the effects of changes of solvent on the Arrhenius parameters for the decomposition of phenylazotriphenylmethane (see Table 7; also Alder and Leffler [13] and Leffler and Hubbard [14]) is the parallelism exhibited between the energies and entropies of activation. The variations in energy of activation are compensated by the variations in entropy of activation, and only a very small and irregular solvent effect on the rate of reaction results (see Table 3). Parallel variation of E and ΔS^* has been observed in the past in other reactions (see, for example, Fairclough and Hinshelwood,[33] and Raine and Hinshelwood [34]), and has been discussed by Ingold.[35] The last-named author points out that solvation of an ion or molecule must lead to stabilisation, since work is done by the molecule in orientating itself and attracting the molecules

[33] Fairclough and Hinshelwood, *J.*, 1938, 236.
[34] Raine and Hinshelwood, *J.*, 1939, 1378.
[35] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, New York, 1953, p. 345.

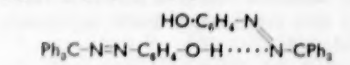
of the solvent. It follows that a change from a less polar to a more polar solvent should decrease or increase the activation energy of a reaction according as the transition state is more or less polar than the reactants. There may be compensating changes of entropy, for solvation, although it reduces energy, may increase the organisation of solvent molecules, thereby decreasing the probability of the solvated state. Thus, for example, in the present reaction, if the formation of the activated complex is accompanied by desolvation, then a change of solvent to one in which the extent of desolvation is greater must involve an increase in the energy of activation, and probably a parallel increase in the entropy of activation, since an increase in the degree of solvation must certainly result in the restriction of the " freedom " of the reacting molecules.

Neglecting, for the moment, the values of E and $\Delta S^{\ddagger}$ obtained for the reaction in *n*-propyl alcohol, it is apparent from the results recorded in Table 7 that the above argument may be applied to the present example since, although the errors involved are large compared with the differences in the parameters, the values of E and $\Delta S^{\ddagger}$ for nitromethane, which possesses the highest dielectric constant for the solvents used, are markedly greater than those for nitrobenzene, toluene, and acetic acid. Thus the values of E and $\Delta S^{\ddagger}$ both increase with the capacity of the solvent for solvation. This conclusion is supported by the work of Alder and Leffler [13] and of Leffler and Hubbard.[14] It is apparent, therefore, that the transition state is solvated less than the initial state.

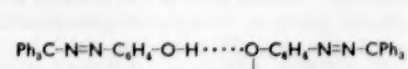
The results obtained for *n*-propyl alcohol are anomalous in that although the dielectric constant of this solvent is lower than that of nitromethane, both the energy and the entropy of activation are greater. Alcohols have in the past been found to be more efficient solvating solvents than aprotic solvents (see, for example, Hughes and Whittingham, quoted by Ingold,[36] who found that the rate of the reaction between trimethylamine and trimethylsulphonium ions varied with the solvent in the order $H_2O < MeOH < EtOH < Me{\cdot}NO_2$, in which the alcohols appear as intermediate with regard to their solvating properties between water and nitromethane). In the present instance the high degree of solvation of phenylazotriphenylmethane by *n*-propyl alcohol may be due to the formation of a hydrogen bond between the alcohol and one of the nitrogen atoms of phenylazotriphenylmethane (III). If the process of activation involves breaking this bond, an increase in activation energy of the required order should be observed. The formation of a hydrogen bond in the intial state would also explain the high value of E (30 kcal. mole^{-1}) obtained by Huisgen and Nakaten [10] for the decomposition of phenylazotriphenylmethane in aniline, and such an explanation has been suggested by these authors. It is also possible that the abnormally high values obtained by Cohen and Wang [12] for the activation energies of the decomposition of *p*-hydroxyphenylazotriphenylmethane in toluene, acetic acid, and pyridine may be due to the formation of hydrogen bonds between two molecules of *p*-hydroxyphenylazotriphenylmethane, giving complexes of the types of (IV) and (V) :



(III)

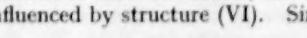


(IV)



(V)

In addition to the contributions of these structures, the value of E for the decomposition in pyridine may also be influenced by structure (VI). Similar considerations may also be



(VI)

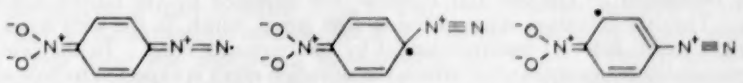
applied to the decomposition of *p*-acetamidophenylazotriphenylmethane. The activation energy in this case is 30 kcal. mole^{-1}, and the high value may be attributed to the formation of hydrogen bonds between the –NH– group of one molecule and either the azo- or the carbonyl group of another.

[36] Ref. 35, p. 350.

The formation of hydrogen-bonded complexes of this type must necessarily lead to an increase, not only in the energy, but also in the entropy of activation, since it must result in a certain restriction in the randomness of distribution and orientation of the reacting molecules. This expectation is also fulfilled by the evidence available.

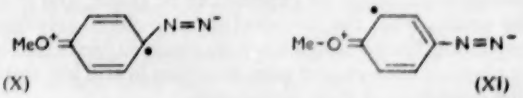
The formation of complexes between reagent and solvent by the influence of electrostatic forces has been used by Cohen, Leffler, and Barbato [15] to explain their otherwise anomalous results concerning the decomposition of *p*-nitrophenylazotri-*p*-methoxyphenylmethane in benzonitrile and veratrole.

Substituent Effects.—The results given in Tables 8 and 4, and those of Cohen and Wang [12] show that, so far as is known, all substituent groups except methyl, when present in the *para*-position of the single phenyl nucleus, increase both the energy and the entropy of activation, and that these increases tend to compensate each other, as in the case of solvent variation, so that, in the temperature range studied, these various compounds all decompose at comparable rates. The lack of any simple relation between the polar characteristics of the substituent groups and their effect on the activation parameters indicates that these groups must be capable of influencing the reaction in more than one way. Cohen and Wang [12] attempted to explain the increase in activation energy occasioned by both electron-attracting and electron-repelling groups as being due to the stabilisation of the initial states by resonance in the presence of substituents of both types. However, there seems to be no reason why this effect should not work in the opposite direction, since an even greater stabilisation of the arylazo-radicals resulting from the primary dissociation, and hence of the transition state for the dissociation, would be expected by virtue of the contribution of canonical forms of the types (VII), (VIII), and (IX) in the presence of



(VII) (VIII) (IX)

substituents having $-T$ effects, such as the nitro-group, and (X) and (XI) in the presence of substituents which display $+T$ effects, such as the methoxy-group. In any event, such an explanation, while it obviously must play a part, cannot be sufficient to explain the whole observed series of substituent effects, especially when the substituents are orientated ***meta*** to the azo-group, when canonical structures of this type cannot be written, and no stabilisation of either the initial or the transition state by resonance involving the substituent group is possible. There must therefore be a further mechanism whereby any substituent present can influence the activation parameters.



(X) (XI)

It is clear from the above consideration of solvent effects that the degree of desolvation which accompanies the formation of the transition state must exert a considerable influence on the activation parameters. The greater the extent of solvation of the initial state, the greater will be the desolvation which may take place, and hence the greater the increase in E and $\Delta S^{\ddagger}$ which is occasioned. Thus it seems likely that a correlation should exist between the effect of a substituent on the degree of solvation of the reagent, by virtue of its effect on the polarisation of the reagent, and its effect on the activation parameters.

A detailed consideration of the effects of substituents on the solvation of arylazotriarylmethanes presupposes a knowledge of the magnitude and direction of the dipole moment of phenylazotriphenylmethane. This compound would be expected to possess a dipole moment, because Bergmann, Engel, and Wolff [37] have found that the dipole moment of triphenylmethane in carbon disulphide solution has the value 0·62 D. Moreover, an

[37] Bergmann, Engel, and Wolff, *Z. phys. Chem.*, 1932, **17**, *B*, 81.

indication of the polarity of the Ph–N=N system is provided by the dipole moment of *cis*-azobenzene, which has been given [38] as 3·0 D. However, in molecules of this type, where the dipolar centres are widely separated, it is not certain that the total dipole moment should provide a good indication of the extent of the solvation, since it may well be that the dipolar centres are solvated separately. Hence it appears that reliable prediction of the solvation of these molecules is not possible.

Since the effects of substituents in the *para*-position are complicated by resonance stabilisation, which must take place to an uncertain extent, of initial and transition states, it seems likely that the solvation effects might be better illustrated by the *meta*-substituted compounds, in which the resonance effects are minimised. If the above discussion is essentially correct, the effects of *meta*-substituents should therefore depend only on solvation phenomena. The kinetic results given in Table 9 demonstrate that the energy and entropy of activation are increased by both electron-attracting and electron-repelling groups in the *meta*-position. Thus it seems likely that the solvation of the reagent molecule is increased by substituents of both polar types, and that the effect varies in the order Me < Cl < NO_2. This may be due to the separate solvation of the various polar centres in the molecule but, in any case, as is pointed out above, detailed discussion of the factors governing the solvation of such large molecules is, at present, unprofitable.

If it be now assumed that a similar influence on solvation is exerted by these groups when present in the *para*-position, the kinetic results for the decomposition of *para*-substituted arylazotriphenylmethanes can be rationalised if allowance is made for the resonance effects which may now come into play. The results given in Table 8 show that the activation parameters are decreased by the introduction of a *para*-methyl group, virtually unaffected by chlorine and bromine, but increased by the nitro-group in this position. Thus the solvation effect of the methyl group, which, in the *meta*-series exerts the smallest effect, must be counterbalanced by the resonance effect. In the case of the *p*-halogen-substituted compounds in which the solvation effect is expected to be somewhat larger, the two effects balance each other almost exactly, while the highly polar nitro-group exerts a large effect on the solvation, which is not balanced by the resonance effect.

In the series of compounds with substituents in the *para*-positions of the triphenylmethyl group it appears, on the other hand, that resonance is the major factor governing the stability of the compounds. This is not unreasonable, since *para*-substituents are known to exert a profound influence on the dissociation of hexa-arylethanes. Thus hexa-*p*-nitrophenylethane is completely dissociated into free radicals at 5° in benzene solution (Ziegler, quoted by Waters [39]). The results given in Table 10 show that methyl groups in this position exert very little influence on the kinetics of the decomposition and this may be due to the compensation of small resonance and solvation effects. The resonance effect of a halogen substituent might be expected to be larger, and it may be seen that a decrease in stability results from the introduction of *p*-chloro-substituents. The failure to prepare the corresponding bromo- and nitro-compounds suggests that in these compounds the resonance effect plays an even greater part, resulting in still less stable molecules which decompose under the conditions of their preparation.

It is emphasised that the above qualitative discussion is no more than an enumeration of factors which may contribute to the stability of arylazotriarylmethanes, and an attempt to show that, if certain not unreasonable assumptions are made, the influences revealed by the measurement of the activation parameters for the decomposition can be seen to fall into a rational pattern.

Thanks are accorded to the Breconshire County Council Education Committee for the award of a grant to G. L. D.

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[*Received, May 24th, 1956.*]

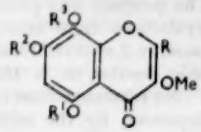
[38] Hartley and Le Fèvre, *J.*, 1939, 531.
[39] Ref. 31, p. 53.

845. *Wessely–Moser Rearrangement of Chromonols and Flavonols.*

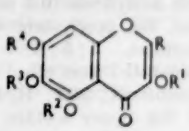
By (Miss) D. M. Donnelly, (Mrs.) E. M. Philbin, and T. S. Wheeler.

5 : 8-Dihydroxy-chromonols and -flavonols, on treatment with hydriodic acid under sufficiently drastic conditions, undergo the Wessely–Moser rearrangement to form the corresponding 5 : 6-dihydroxy-compounds.

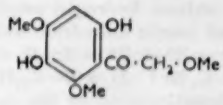
Chakravorty, Mukerjee, Murty, and Seshadri [1] concluded that derivatives of 5 : 8-dihydroxychromonols (*e.g.*, I; R = R^1 = R^2 = R^3 = Me) did not undergo the well-known Wessely–Moser rearrangement [2] to the corresponding 5 : 6-dihydroxychromonol (*e.g.*, II*a*) on treatment with hydriodic acid. 5 : 8-Dihydroxyflavonols were also believed not to



(I)



(II)



(III)

(II) { (*a*) R = Me, R^1 = R^2 = R^3 = R^4 = H
(*b*) R = 3 : 4-$(HO)_2C_6H_3$, R^1 = R^2 = R^3 = R^4 = H.
(*c*) R = R^1 = R^4 = Me, R^2 = R^3 = Ac.
(*d*) R = R^3 = R^4 = Me, R^1 = R^2 = Ac.
(*e*) R = R^1 = R^4 = Me, R^2 = R^3 = H.
(*f*) R = R^2 = R^4 = Me, R^1 = R^3 = H.
(*g*) R = 3 : 4-$(MeO)_2C_6H_3$, R^1 = R^3 = R^4 = Me, R^2 = H.

undergo this transformation [3] although an observation by Briggs and Locker [4] indicated that the gossypetin ether, ternatin (I; R = 4-hydroxy-3-methoxyphenyl, R^1 = H, R^2 = R^3 = Me), on demethylation by hydriodic acid in phenol rearranged to give quercetagetin (II*b*). This result was unexpected as meliternin (I; R = 3 : 4-methylenedioxyphenyl, R^1 = R^2 = R^3 = Me) yielded gossypetin (5 : 7 : 8 : 3′ : 4′-pentahydroxyflavonol) under the same conditions.

It has now been found [5] that, on demethylation by hydriodic acid under pressure, both 5 : 7 : 8-trihydroxy-3-methoxy-2-methylchromone (I; R = Me, R^1 = R^2 = R^3 = H) and 5 : 7 : 8-trihydroxy-3 : 3′ : 4′-trimethoxyflavone (I; R = 3 : 4-dimethoxyphenyl, R^1 = R^2 = R^3 = H) give, respectively, 5 : 6 : 7-trihydroxy-2-methylchromonol (II*a*) and quercetagetin (II*b*).

The preparation of an authentic sample of 5 : 6 : 7-trihydroxy-2-methylchromonol (II*a*) involved, as a first stage, Kostanecki acylation of 3 : 6-dihydroxy-ω : 2 : 4-trimethoxyacetophenone (III). Analysis of the product indicated that one methoxyl group had been demethylated during the fusion.[2a] The formation of 5 : 6-diacetoxy-3 : 7-dimethoxy-2-methylchromone (II*c*) was shown by the following considerations. Whether dealkylation occurred before or after cyclic acylation, the methoxyl group in the 7-position is most likely to remain. This assumption leaves for discussion three possible structures (I; R = R^2 = Me, R^1 = R^3 = Ac), (II*c*), and (II*d*) for the diacetoxydimethoxymethylchromone formed. Examination of the deacylated chromone showed that it was not 5 : 8-dihydroxy-3 : 7-dimethoxy-2-methylchromone (I; R = R^2 = Me, R^1 = R^3 = H) already described by Chakravorty and his co-workers.[1] Of the remaining two possible dihydroxy-isomers, 5 : 6-dihydroxy-3 : 7-dimethoxy- (II*e*) and 3 : 6-dihydroxy-5 : 7-dimethoxy-2-methylchromone (II*f*), the former (a catechol derivative) was shown to be present by its retardation when run on borate-buffered paper. This test is diagnostic for *ortho*-hydroxyl groups.[6] The chromone did not fluoresce in ultraviolet light, thus confirming the absence of a 3-hydroxyl group.[7]

[1] Chakravorty, Mukerjee, Murty, and Seshadri, *Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 37.
[2] (*a*) Wessely and Moser, *Monatsh.*, 1930, **56**, 97; (*b*) cf. Gallagher, Hughes, O'Donnell, Philbin, and Wheeler, *J.*, 1953, 3770.
[3] Seshadri, Varadarajan, and Venkateswarlu, *Proc. Indian Acad. Sci.*, 1950, **32**, *A*, 251.
[4] Briggs and Locker, *J.*, 1949, 2157.
[5] Cf. Donnelly, Philbin, and Wheeler, *Chem. and Ind.*, 1953, 567; 1954, 163.
[6] Wachtmeister, *Acta Chem. Scand.*, 1951, **5**, 976.
[7] Swain, *Chem. and Ind.*, 1954, 1480.

Experimental

Derivatives of **5 : 6 : 7**-*Trihydroxy*-**2**-*methylchromonol* (IIa).—A mixture of **3 : 6**-dihydroxy-**ω : 2 : 4**-trimethoxyacetophenone [8] (III) (0·5 g.), acetic anhydride (1·4 ml.), and anhydrous sodium acetate (0·8 g.) was heated at 170° for 4 hr. The product was triturated with water. The residual **5 : 6**-*diacetoxy*-**3 : 7**-*dimethoxy*-**2**-*methylchromone* (IIc) formed pale yellow needles (0·1 g.) (from ligroin–ethanol), m. p. 141° (Found : C, 57·2, 56·8; H, 4·9, 4·9. $C_{16}H_{16}O_8$ requires C, 57·1; H, 4·8. Calc. for $C_{15}H_{16}O_7$: C, 58·4; H, 5·2%). This was deacylated by treatment on a steam-bath with ethanolic hydrochloric acid for 30 min. The resulting solution was diluted with water and **5 : 6**-*dihydroxy*-**3 : 7**-*dimethoxy*-**2**-*methylchromone* (IIe) was collected in ether. It separated from ethanol in needles, m. p. 182° (Found : C, 57·6; H, 5·0; OMe, 23·8. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8; 2OMe, 24·6%). The ethanolic ferric colour was green.

The diacetoxydimethoxymethylchromone (0·2 g.) was refluxed at 135—140° for 1½ hr. with hydriodic acid (*d* 1·7; 3 ml.) and acetic anhydride (0·5 ml.). The product was poured into aqueous sodium hydrogen sulphite, and the precipitate was crystallised from ethanol and acetylated (acetic anhydride–sodium acetate). **3 : 5 : 6 : 7**-*Tetra-acetoxy*-**2**-*methylchromone* (II; $R^1 = R^2 = R^3 = R^4 =$ Ac, R = Me) separated from ethyl acetate in needles, m. p. 168—169° (Found : C, 55·1; H, 4·0. $C_{18}H_{16}O_{10}$ requires C, 55·1; H, 4·1%). No rearrangement occurred during demethylation as the m. p. of the above acetate was depressed by the addition of **3 : 5 : 7 : 8**-tetra-acetoxy-2-methylchromone (see next paragraph).

Derivatives of **5 : 7 : 8**-*Trihydroxy*-**2**-*methylchromonol.* A mixture of **5 : 7 : 8**-trihydroxy-3-methoxy-2-methylchromone [1] (I; R = Me, $R^1 = R^2 = R^3 =$ H) (Found : C, 48·3; H, 5·2. Calc. for $C_{11}H_{10}O_6,2H_2O$: C, 48·2; H, 5·2%) (0·2 g.), aluminium chloride (2 g.), and sodium chloride (0·5 g.) was heated for 2 min. at 180° (method of Bruce, Sorrie, and Thomson [9]), and the product was decomposed by ice and hydrochloric acid. The chromonol separated from ethanol in aggregates (0·12 g.), m. p. 248° (decomp.) (Found : C, 53·9; H, 4·0. Calc. for $C_{10}H_8O_6$: C, 53·6; H, 3·6%). Chakravorty and his co-workers [1] state that **5 : 7 : 8**-trihydroxy-2-methylchromonol becomes brown at 250° and decomposes at 270—273°. **3 : 5 : 7 : 8**-*Tetra-acetoxy*-**2**-*methylchromone* was crystallised successively from ethyl acetate and ethanol. It formed pale yellow needles, m. p. 179—180° (Found : C, 54·9; H, 4·3. $C_{18}H_{16}O_{10}$ requires C, 55·1; H, 4·1%). The m. p. was depressed to 156—160° by addition of **3 : 5 : 6 : 7**-tetra-acetoxy-2-methylchromone, m. p. 168—169° (see above).

The absence of rearrangement in the demethylation was confirmed by remethylation of the chromonol (methyl sulphate–acetone–potassium carbonate) which gave **3 : 5 : 7 : 8**-tetramethoxy-2-methylchromone, m. p. and mixed m. p.,[1] 158—159°.

Rearrangement of **5 : 7 : 8**-*Trihydroxy*-**3**-*methoxy*-**2**-*methylchromone.*—This chromone (0·2 g.) was heated with hydriodic acid (*d* 1·7; 5 ml.) and phenol (4·5 ml.) for 1 hr. at 170—180°. The product was treated with aqueous sodium hydrogen sulphite. The precipitate separated from ethanol in aggregates, m. p. *ca.* 300°. On acetylation (sodium acetate–acetic anhydride) it gave **3 : 5 : 6 : 7**-tetra-acetoxy-2-methylchromone, m. p. and mixed m. p. 169°.

Rearrangement of Gossypetin.—(a) *Demethylation at ordinary pressure.* **5 : 7**-Dihydroxy-**3 : 3′ : 4′**-trimethoxyflavone (from acetic acid) had m. p. 248—250° (Allan and Robinson [10] give m. p. 240—245°) (Found : C, 63·2; H, 4·7. Calc. for $C_{18}H_{16}O_7$: C, 62·8; H, 4·7%). Persulphate hydroxylation of this compound gave **5 : 7 : 8**-trihydroxy-**3 : 3′ : 4′**-trimethoxyflavone (I; R = **3 : 4**-dimethoxyphenyl, $R^1 = R^2 = R^3 =$ H) [11] which (0·4 g.) was heated for 3 hr. at 150—160° with hydriodic acid (*d* 1·7; 15 ml.) and phenol (4·5 ml.) in an atmosphere of carbon dioxide. The product was poured into aqueous sodium hydrogen sulphite, and the resulting precipitate was crystallised from aqueous ethanol and acetylated (sodium acetate–acetic anhydride). The acetyl derivative [4] separated from ethanol and ethyl acetate in needles, m. p. 215—220°, depressed by addition of **3 : 5 : 6 : 7 : 3′ : 4′**-hexa-acetoxyflavone [8] (hexa-*O*-acetylquercetagetin; m. p. 211—212°) but raised to 227—228° by addition of **3 : 5 : 7 : 8 : 3′ : 4′**-hexa-acetoxyflavone [12] (hexa-*O*-acetylgossypetin; m. p. 228—230°) (Found : C, 57·0; H, 4·2. Calc. for $C_{27}H_{22}O_{14}$: C, 56·8; H, 3·9%). A solution of the hexa-acetoxyflavone in sulphuric acid exhibited a green fluorescence in ultraviolet light similar to that shown by hexa-*O*-acetylquercetagetin, indicating the presence of a trace of this compound. Hexa-*O*-acetylgossypetin does not fluoresce in sulphuric acid solution.

[8] Row and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 23.
[9] Bruce, Sorrie, and Thomson, *J.*, 1953, 2403.
[10] Allan and Robinson, *J.*, 1926, 2336.
[11] Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1947, **25**, *A*, 417.
[12] Baker, Nodzu, and Robinson, *J.*, 1929, 74.

In the synthesis of hexa-*O*-acetylquercetagetin, the intermediate compound 6-hydroxy-3 : 5 : 7 : 3′ : 4′-pentamethoxyflavone (IIg) (Found : C, 61·8; H, 5·3. Calc. for $C_{20}H_{20}O_8$: C, 61·9; H, 5·2%) was found to have m. p. 245° (from ethanol) : Row and Seshadri [8] give m. p. 209—210°.

No rearrangement occurred when 5 : 7 : 8-trihydroxy-3 : 3′ : 4′-trimethoxyflavone (see above) was demethylated by aluminium chloride in benzene in the usual way. The product on acetylation (sodium acetate–acetic anhydride), and remethylation (methyl sulphate–acetone–potassium carbonate), gave hexa-*O*-acetyl- and hexa-*O*-methyl-gossypetin, respectively. The identity of each product was confirmed by mixed m. p. determinations.[11, 12]

(b) *Rearrangement experiments.* A mixture of 5 : 7 : 8-trihydroxy-3 : 3′ : 4′-trimethoxyflavone or of gossypetin (0·2 g.), hydriodic acid (*d* 1·7; 9 ml.), and phenol (4·5 ml.) was heated for 1½ hr. at 180—190°, and the product was mixed with aqueous sodium hydrogen sulphite. The precipitate separated from ethanol in yellow plates, m. p. 306—310°. The acetyl derivative crystallised from ethyl acetate in needles, m. p. 210°, not depressed by addition of hexa-*O*-acetylquercetagetin.

The compound, m. p. 306—310°, gave on remethylation (methyl sulphate–potassium carbonate–acetone) hexa-*O*-methylquercetagetin,[12, 13] m. p. and mixed m. p. 141° and 157° (dimorphic).

One of us (D. M. D.) thanks Dr. Michael J. Walsh and the authorities of University College, Dublin, for the grant of a Michael J. Walsh Research Fellowship.

UNIVERSITY COLLEGE, DUBLIN. [*Received, June 4th*, 1956.]

[13] Perkin, *J.*, 1913, **103**, 209.

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846. *Thermal Cyclization of o-Aroyloxyacetoarones. Part III.* Synthesis in the Chromone Series.*

By T. M. O'TOOLE and T. S. WHEELER.

The method for the preparation of flavones and flavonol ethers based on thermal cyclization of aroyl esters of *o*-hydroxyacetoarones * has been extended to the synthesis of chromonol ethers. It is confirmed that this method involves a thermal Baker–Venkataraman transformation.

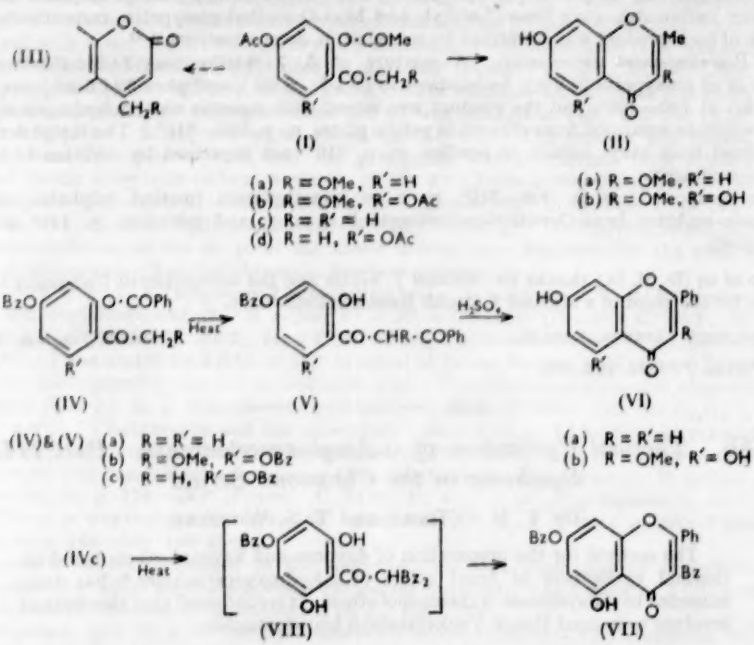
IT was shown in Part I [1] that *o*-aroyloxyacetoarones yield flavones when heated in glycerol; in some instances the yield is excellent.[2] Flavonol 3-methyl ethers can also be synthesised in this way.[3] The method has now been extended to the synthesis of 7-hydroxy- and 5 : 7-dihydroxy-3-methoxy-2-methylchromone (IIa and b) from the corresponding acetoxy-ω-methoxyacetophenones (Ia) and (Ib), respectively.

In view of the possibility of coumarin formation (see III), the identity of each chromone derivative was confirmed by comparison with an authentic specimen prepared by Kostanecki–Robinson acylation of the related *o*-hydroxyacetophenones.[4] These chromonol ethers were also synthesized by the Baker–Venkataraman method, spontaneous cyclization of the intermediate diketone occurring in the transformation. No useful result was obtained by application of the glycerol cyclization technique to 2-acetoxy-4-benzyloxyacetophenone, 2 : 4-diacetoxyacetophenone (Ic) or 2 : 4 : 6-triacetoxyacetophenone (Id). Also, it was not found possible to obtain 2-styrylchromones from *o*-cinnamoyloxyacetophenone, 4-benzyloxy-2-cinnamoyloxyacetophenone, or 2 : 4 : 6-tricinnamoyloxyacetophenone, by thermal cyclization in glycerol, although these esters undergo the Baker–Venkataraman transformation to form the corresponding 2-styrylchromones, and *o*-cinnamoyloxyacetophenones had previously been cyclized by the glycerol method, though in poor yield.[1] Two of the styrylchromones were oxidized to chromonecarboxylic acids.

* Parts I and II, *J.*, 1950, 1252; 1952, 2063.

[1] Dunne, Gowan, Keane, O'Kelly, O'Sullivan, Roche, Ryan, and Wheeler, *J.*, 1950, 1252.
[2] Cf. Wheeler, *Org. Synth.*, 1952, **32**, 72.
[3] Lynch, O'Toole, and Wheeler, *J.*, 1952, 2063.
[4] (*a*) Allan and Robinson, *J.*, 1924, 2192; (*b*) Kalff and Robinson, *J.*, 1925, 1968.

Thermal Baker–Venkataraman Transformation.—The suggestion [1,3] that the glycerol cyclization involves a thermal Baker–Venkataraman transformation receives support from the observation that 2 : 4-dibenzoyloxyacetophenone (IVa), and 2 : 4 : 6-tribenzoyloxy-ω-methoxyacetophenone (IVb) are transformed, when heated, into the diketones, ω-benzoyl-4-benzoyloxy-2-hydroxyacetophenone (Va), and ω-benzoyl-4 : 6-dibenzoyloxy-2-hydroxy-ω-methoxyacetophenone (Vb), respectively. The diketones cyclized to the corresponding



hydroxyflavones (VIa and b) on treatment with sulphuric acid in the usual way. 2 : 4 : 6-Tribenzoyloxyacetophenone (IVc) gave, on heating, 3-benzoyl-7-benzoyloxy-5-hydroxyflavone (VII) with, presumably, intermediate formation of the triaroylmethane (VIII). Baker [5] observed a similar double Baker–Venkataraman transformation with cyclization when he treated 2 : 6-dibenzoyloxyacetophenone with potassium carbonate in toluene and obtained 3-benzoyl-5-hydroxyflavone. The structure of compound (VII) was confirmed by the identity of its 5-*O*-benzoyl derivative with the product of Allan–Robinson benzoylation of phloracetophenone with omission of the normal alkaline after-boil.

Experimental

Crystallization was from ethanol unless otherwise stated.

Preparation of Chromonols.—**3 : 7-*Dihydroxy-2-methylchromone.*** **2 : 4-*Diacetoxy-ω-methoxyacetophenone*** (Ia), needles, m. p. 54° (Found : C, 58·7; H, 5·3. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%), which was prepared by the pyridine–acetic anhydride method, was heated in anhydrous glycerol (10 parts) at 250° in an atmosphere of nitrogen for 30 min. The product was diluted with water (100 parts), and the resulting precipitate was chromatographed from ethanol on alumina. The yellow band of 7-hydroxy-3-methoxy-2-methylchromone (IIa) was extracted by boiling ethanol. It separated from aqueous ethanol in needles (0·1 part), m. p. 214° (Found : C, 63·8; H, 4·7. Calc. for $C_{11}H_{10}O_4$: C, 64·1; H, 4·9%), not depressed by addition of an authentic sample obtained by Kostanecki–Robinson acylation of ω-methoxyresacetophenone.[4a]

The hydroxymethoxymethylchromone was also prepared by the Baker–Venkataraman

[5] Baker, *J.*, 1934, 1953.

method. A solution of 2 : 4-diacetoxy-ω-methoxyacetophenone (1 g.) in pyridine (10 ml.) was shaken with powdered potassium hydroxide (0·2 g.) for 2 hr., and the product was acidified to yield the crude chromone which, after crystallization (0·1 g.), did not depress the m. p. of an authentic sample. Demethylation of this chromone by hydriodic acid gave 3 : 7-dihydroxy-2-methylchromone, m. p. 249° (decomp.) (Found : C, 62·6; H, 4·5. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%). Allan and Robinson [4a] give the same m. p.

3 : 7-*Dimethoxy-2-styrylchromone*. A mixture of 3 : 7-dimethoxy-2-methylchromone (1 g.), benzaldehyde (2 ml.), and ethanolic sodium ethoxide (Na, 0·5 g.; EtOH, 10 ml.) was refluxed for 30 min. 3 : 7-*Dimethoxy-2-styrylchromone* crystallized in yellow needles, m. p. 157—158° (Found : C, 73·8; H, 5·2. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%).

3 : 5 : 7-*Trihydroxy-2-methylchromone*. 2 : 4 : 6-*Triacetoxy-ω-methoxyacetophenone* (Ib), plates, m. p. 115—116° (Found : C, 55·7; H, 5·1. $C_{15}H_{16}O_8$ requires C, 55·6; H, 5·0%), gave 5 : 7-dihydroxy-3-methoxy-2-methylchromone (IIb), m. p. 223—224° (Found : C, 59·4; H, 4·6. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%), by both the glycerol dehydration and the Baker–Venkataraman method, in about 50% yield (crystallized material). The products did not depress the m. p. of an authentic sample of the dihydroxymethoxychromone.[4b] For demethylation the chromone (1 g.) was refluxed with hydriodic acid (*d* 1·7; 20 ml.) for 45 min., and the product was poured into aqueous sodium hydrogen sulphite. The precipitate of 3 : 5 : 7-*trihydroxy-2-methylchromone* separated from aqueous ethanol in needles (0·5 g.), m. p. 224° (Found : C, 57·3; H, 4·0. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%). The m. p. was depressed by addition of 5 : 7-dihydroxy-3-methoxy-2-methylchromone, m. p. 224°.

2-*Acetoxy-4-benzyloxyacetophenone*, plates, m. p. 111—112° (Found : C, 71·9; H, 5·7. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%), was prepared by the pyridine–acetic anhydride method from 2-hydroxy-4-benzyloxyacetophenone.[5]

Attempted Cyclization in Glycerol of o-*Cinnamoyloxyacetophenones*.—The following esters were prepared by the pyridine–acid chloride method : *o*-cinnamoyloxyacetophenone, needles, m. p. 73° (Found : C, 76·1; H, 5·4. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%) (Doyle *et al.*[7] give the same m. p.); 4-*benzyloxy-2-cinnamoyloxyacetophenone*, needles, m. p. 102—103° (Found : C, 77·6; H, 5·4. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%); 2 : 4 : 6-*tricinnamoyloxyacetophenone*, m. p. 178—180° (Found : C, 75·1; H, 4·5. $C_{35}H_{26}O_7$ requires C, 75·3; H, 4·7%). No useful result was obtained by the application of the glycerol dehydration method to these esters.

Synthesis of 2-*Styrylchromones by the Baker–Venkataraman Method*.—4-Benzyloxy-2-cinnamoyloxyacetophenone was heated with pyridine and potassium hydroxide in the usual way. The product, 7-benzyloxy-2-styrylchromone, had m. p. 162—163° (from benzene or acetic acid), not depressed by addition of an authentic sample.[6] Similarly, 2 : 4 : 6-tricinnnamoyloxyacetophenone gave 5 : 7-dicinnamoyloxy-2-styrylchromone, m. p. 232°, not depressed by addition of an authentic sample.[8]

Oxidation of 2-*Styrylchromones to Chromone-2-carboxylic Acids*.—A solution of 7-benzyloxy-2-styrylchromone (1 g.) in pyridine (10 ml.) and water (100 ml.) was treated with aqueous potassium permanganate (1 g. in 50 ml.).[9] The product was decolorized by sulphur dioxide, concentrated to half-volume under reduced pressure, acidified, and extracted with ethyl acetate. 7-*Benzyloxychromone-2-carboxylic acid* was removed from the extract by aqueous sodium carbonate and recovered by acidification. It separated in needles (0·2 g.), m. p. 237° (Found : C, 68·7; H, 4·3. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%).

Decarboxylation and debenzylation was effected by refluxing the benzyloxychromone-carboxylic acid in glacial acetic acid saturated with hydrogen bromide for 2 hr.[9] Dilution of the product with water afforded 7-hydroxychromone, m. p. 218°. Kostanecki *et al.*[10] give the same m. p.

2-Styrylchromone when similarly oxidized gave chromone-2-carboxylic acid, m. p. 247—248° (Found : C, 63·4; H, 3·5. Calc. for $C_{10}H_6O_4$: C, 63·2; H, 3·2%). Heywang and Kostanecki [11] give m. p. 252°. Gomberg and Cone [12] give m. p. 258°. Decarboxylation by the method of Ruhemann and Stapleton [13] gave, as they describe, chromone, m. p. 59°.

Thermal Baker–Venkataraman Reaction.—The *o*-aroyloxyacetophenone was heated for 30 min.

[6] Gulati, Seth, and Venkataraman, *J.*, 1934, 1765.
[7] Doyle, Gógan, Gowan, Keane, and Wheeler, *Sci. Proc. Roy. Dublin Soc.*, 1948, **24**, 291.
[8] Cheema, Gulati, and Venkataraman, *J.*, 1932, 925.
[9] Cf. Baker, Robinson, and Simpson, *J.*, 1937, 805.
[10] Kostanecki, Paul, and Tambor, *Ber.*, 1901, **34**, 2475.
[11] Heywang and Kostanecki, *Ber.*, 1902, **35**, 2887.
[12] Gomberg and Cone, *Annalen*, 1910, **376**, 229.
[13] Ruhemann and Stapleton, *J.*, 1900, **77**, 1179.

at 280°/3 mm., and the diketone formed was extracted from the residue with ethanol. 2 : 4-Dibenzoyloxyacetophenone (IVa) [14] (2 g.) gave ω-benzoyl-4-benzoyloxy-2-hydroxyacetophenone (Va), yellow needles (0·25 g.), m. p. 167°, not depressed by addition of an authentic sample.[14] Cyclization by sulphuric acid gave 7-hydroxyflavone (VIa) (mixed m. p.).

2 : 4 : 6-Tribenzoyloxy-ω-methoxyacetophenone (IVb) [3] (3 g.) gave *ω-benzoyl-4 : 6-dibenzoyloxy-2-hydroxy-ω-methoxyacetophenone* (Vb), yellow needles (0·5 g.) (from ligroin), m. p. 152—154° (Found : C, 70·8; H, 4·2. $C_{30}H_{22}O_8$ requires C, 70·6; H, 4·3%). The ethanolic ferric reaction was red. This diketone on cyclization by sulphuric acid yielded 5 : 7-dihydroxy-3-methoxyflavone (galangin 3-methyl ether) (VIb), m. p. 297°, not depressed by addition of an authentic sample.[3]

2 : 4 : 6-Tribenzoylacetophenone (IVc) [15](3 g.) gave, when heated, *3-benzoyl-7-benzoyloxy-5-hydroxyflavone* (VII) as a microcrystalline powder (0·2 g.), m. p. 154° (from ligroin) (Found : C, 75·3; H, 3·9. $C_{30}H_{18}O_6$ requires C, 75·3; H, 3·9%). The first fraction from ligroin separated as a yellow powder which melted indefinitely from 58° to 128° (?cyclization), and gave analytical figures for the triketone, *dibenzoyl-4-benzoyloxy-2 : 6-dihydroxybenzoylmethane* (VIII) (Found : C, 72·5, 72·5; H, 4·4, 4·3. $C_{29}H_{20}O_7$ requires C, 72·5; H, 4·2%). Benzoylation (pyridine–benzoyl chloride) of the benzoylflavone, m. p. 154°, gave 3-benzoyl-5 : 7-dibenzoyloxyflavone as a microcrystalline powder (Found : C, 76·6, 76·7; H, 4·2, 4·0. Calc. for $C_{36}H_{22}O_7$: C, 76·3; H, 3·9%), m. p. and mixed m. p. with authentic sample, 173—175°. Dunne *et al.*[1,16] give m. p. 169°.

5 : 7-*Dibenzoyloxyflavone* (Found : C, 75·1; H, 4·0. $C_{29}H_{18}O_6$ requires C, 75·3; H, 3·9%) separated as a crystalline powder, m. p. 194—196°.

UNIVERSITY COLLEGE, DUBLIN. [*Received, June 8th*, 1956.

[14] Baker, *J.*, 1933, 1381.
[15] Canter, Curd, and Robertson, *J.*, 1931, 1245.
[16] Cf. Trivedi, Sethna, and Shah, *J. Indian Chem. Soc.*, 1943, **20**, 171.

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847. *Studies of Sultones.*

By (MRS.) E. M. PHILBIN, E. R. STUART, R. F. TIMONEY, and T. S. WHEELER.

Sultones are obtained by treatment of *o*-acetylphenyl methane- or toluene-ω-sulphonate (I; R = H or Ph) with potassium hydroxide and pyridine.

NOWLAN, SLAVIN, and WHEELER [1] were unable to effect a Baker–Venkataraman rearrangement with *vic*-acetylnaphthyl arenesulphonates. It has now been found that treatment of *o*-acetylphenyl toluene-ω-sulphonate (I; R = Ph) with potassium hydroxide in pyridine yields 2-hydroxy-2-*o*-hydroxyphenyl-1-phenylpropane-1-sulphonic sultone (II) and, by prolonged action, 2-*o*-hydroxyphenyl-1-phenylprop-1-ene-1-sulphonic sultone (III; R = Ph). The structure of the former product was confirmed by analysis and by reactions (shown in the diagram) which yielded compounds (III; R = Ph), (IV), (V; R = Ph), and (VI). Further, the infrared spectra of the first three of these compounds confirm the structure (II) and exclude the alternative structure (I*a*). The formation of the sultone (III) is analogous to the production of coumarins by the Kostanecki–Robinson method from *o*-acetylaryl acetates,[2] and to the synthesis of 2-hydroxyquinolines from *o*-acylaminoacetophenones of the type *o*-C_6H_4(NH·CO·CH_2R)·COMe by the Camps reaction.[3]

2-*o*-Hydroxyphenyl-1-phenylpropanesulphonic sultone (V; R = Ph), m. p. 107—108°, gave by refluxing with aqueous sodium hydroxide an isomer (VIII), m. p. 158—160°. The infrared spectra of compounds (V; R = Ph) and (VIII) differed slightly. That of the former had bands for the sulphonyloxy-function at 1152 and 1171 cm.$^{-1}$, while compound

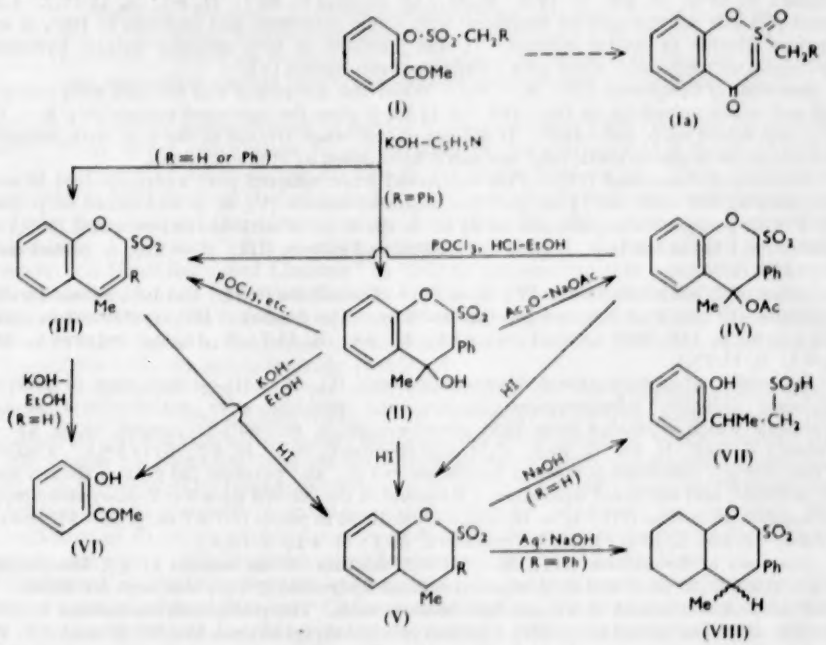
[1] Nowlan, Slavin, and Wheeler, *J.*, 1950, 340.
[2] Heilbron, Hey, and Lythgoe, *J.*, 1936, 295.
[3] Camps, *Ber.*, 1899, **32**, 3228.

(VIII) had a single band for the same function at 1169 cm.$^{-1}$. It is suggested that alkaline enolic epimerisation occurred, and that these compounds are geometrical isomers.

Infrared spectra.

Compound	$-O-SO_2-$ Bands (cm.$^{-1}$)		Compound	$-O-SO_2-$ Bands (cm.$^{-1}$)
	1145—1200 (s)	1330—1420 (s)		
II; R = Ph	1164, 1348, 1384		IV; R = Ph	1173, 1364
III; R = Ph ...	1164, 1372, 1384		V; R = Ph	1152, 1171, 1368
			VIII	1169, 1363

o-Acetylphenyl methanesulphonate (I; R = H) gave with potassium hydroxide and pyridine 2-*o*-hydroxyphenylprop-1-ene-1-sulphonic sultone (III; R = H), which with ethanolic alkali yielded *o*-hydroxyacetophenone (VI), and reacted as shown in the diagram to yield compound (V; R = H), and the acid (VII) which was characterised as the *S*-benzylthiuronium salt.



o-Acetylphenyl benzenesulphonate and toluene-*p*-sulphonate remained unchanged when treated with potassium hydroxide and pyridine. Attempts to effect the Baker–Venkataraman transformation of a number of *o*-acetylphenyl aroates using acid catalysts proved unsuccessful.

Experimental

Ethanol was employed for crystallisation if no solvent is mentioned.

Derivatives of o-Acetylphenyl Toluene-ω-sulphonate (I; R = Ph).—The product of the interaction of toluene-ω-sulphonyl chloride (5 g.), *o*-hydroxyacetophenone (3·5 g.), and pyridine (25 g.) was *o-acetylphenyl toluene-ω-sulphonate* which crystallised in plates (2·8 g.), m. p. 85—86° (Found: C, 61·9; H, 4·9; S, 10·9. $C_{15}H_{14}O_4S$ requires C, 62·1; H, 4·9; S, 11·0%). A mixture of this compound (5 g.), powdered potassium hydroxide (1 g.), and pyridine (25 g.) was shaken for 48 hr., acidified, and extracted with ether. Removal of the solvent gave *2-hydroxy-2-o-hydroxyphenyl-1-phenylpropane-1-sulphonic sultone* (II) which separated in prisms (2·3 g.), m. p. 202—203° (Found: C, 61·9; H, 5·1; S, 11·0. $C_{15}H_{14}O_4S$, see above). When the

toluenesulphonate was similarly treated with powdered potassium hydroxide and pyridine for 14 days it gave *2-o-hydroxyphenyl-1-phenylprop-1-ene-1-sulphonic sultone* (III; R = Ph), which crystallised in prisms (4·6 g.), m. p. 173—174° (Found: C, 66·2; H, 4·5; S, 11·5. $C_{15}H_{12}O_3S$ requires C, 66·2; H, 4·4; S, 11·8%).

Reactions of Compound (II).—A mixture of the sultone (II) (5 g.) and phosphorus oxychloride (35 ml.) was refluxed for 2½ hr. The product was compound (III; R = Ph), m. p. and mixed m. p. 173—174°. This compound was also obtained by treatment of the sultone (II) for 14 days with powdered potassium hydroxide and pyridine or with acetic anhydride and perchloric acid (1 drop) for 1½ hr. Acetylation of the sultone (II) by acetic anhydride and sodium acetate gave *2-acetoxy-2-o-hydroxyphenyl-1-phenylpropane-1-sulphonic sultone* (IV) which crystallised from ligroin in prisms, m. p. 148—150° (Found: C, 61·6; H, 5·0; S, 10·3. $C_{17}H_{16}O_5S$ requires C, 61·4; H, 4·9; S, 9·7%). Treatment of the sultone (II) with hydriodic acid in acetic anhydride at 150—160° for 1½ hr. gave *2-o-hydroxyphenyl-1-phenylpropane-1-sulphonic sultone* (V; R = Ph), which crystallised from ligroin in needles, m. p. 107—108° (Found: C, 65·5; H, 4·9; S, 12·2. $C_{15}H_{14}O_3S$ requires C, 65·7; H, 5·1; S, 11·7%). Compound (II) was not changed by treatment with acetic anhydride and pyridine at 100°, or with selenium dioxide in boiling ethanol. It was insoluble in 10% aqueous sodium hydroxide. Hydrolysis with ethanolic alkali gave *o*-hydroxyacetophenone (VI).

Reactions of Compound (III; R = Ph).—When this compound was refluxed with hydriodic acid and acetic anhydride at 150—160° for 1½ hr. it gave the saturated sultone (V; R = Ph), m. p. and mixed m. p. 106—108°. It did not change when treated at the b. p. with potassium permanganate in glacial acetic acid, nor was it hydrolysed by ethanolic alkali.

Reactions of Compound (IV).—This compound when refluxed with hydriodic acid in acetic anhydride at 150—160° for 1½ hr. gave the saturated sultone (V), m. p. and mixed m. p. 106—108°; with phosphorus oxychloride for 2½ hr. at the b. p., or with hydrochloric acid (30%) and ethanol for 1 hr. at the b. p., it gave the unsaturated sultone (III; R = Ph), m. p. and mixed m. p. 173—174°.

Action of Alkali on the Sultone (V; R = Ph).—The sultone (0·5 g.) and 10% aqueous sodium hydroxide (10 ml.) were refluxed together for 3 hr. The *product* (VIII) crystallised in needles (0·3 g.), m. p. 158—160° (Found: C, 65·4; H, 4·8; S, 11·7. $C_{15}H_{14}O_3S$ requires C, 65·7; H, 5·1; S, 11·7%).

Derivatives of o-Acetylphenyl Methanesulphonate (I; R = H).—Interaction of methanesulphonyl chloride, *o*-hydroxyacetophenone, and pyridine gave *o-acetylphenyl methanesulphonate* which separated from light petroleum (b. p. 60—80°) in needles, m. p. 42—44° (Found: C, 50·7; H, 4·5; S, 14·5. $C_9H_{10}O_4S$ requires C, 50·5; H, 4·7; S, 14·9%). A mixture of this (2·5 g.), powdered potassium hydroxide (0·5 g.), and pyridine (30 g.) was shaken for 48 hr., acidified, and extracted with ether. Removal of the solvent gave *2-o-hydroxyphenylprop-1-ene-1-sulphonic sultone* (III; R = H) which crystallised in plates (1·7 g.), m. p. 86—87° (Found: C, 55·2; H, 3·9; S, 16·4. $C_9H_8O_3S$ requires C, 55·1; H, 4·1; S, 16·3%).

Reactions of the Sultone (III; R = H).—A mixture of the sultone (1 g.), benzaldehyde (1 g.), ethanol (25 ml.), and 50% aqueous sodium hydroxide (2·5 g.) was kept for 48 hr. The solid product was added to ice and hydrochloric acid. The precipitate crystallised in yellow needles, m. p. and mixed m. p. with *o*-hydroxyphenyl styryl ketone, 88—89° (Found: C, 80·8; H, 5·5. Calc. for $C_{15}H_{12}O_2$: C, 80·3; H, 5·4%). The sultone was not hydrolysed when refluxed with aqueous sodium hydroxide (15%, 25%, or 35%) for 30 min. Ethanolic alkali gave the phenol (VI). *2-o-Hydroxyphenylpropane-1-sulphonic sultone* (V; R = H), which was obtained when the sultone (III; R = H) was refluxed with hydriodic acid for 1½ hr., separated from ligroin in needles, m. p. 62—64° (Found: C, 54·6; H, 5·1; S, 16·4. $C_9H_{10}O_3S$ requires C, 54·5; H, 5·1; S, 16·2%).

A mixture of the sultone (V; R = H) (1·3 g.) and 10% aqueous potassium hydroxide (15 ml.) was refluxed for 3 hr. The product was added to aqueous *S*-benzylthiuronium chloride. *S-Benzylthiuronium 2-o-hydroxyphenylpropane-1-sulphonate* (see VII) crystallised from aqueous ethanol in plates (1·6 g.), m. p. 171—173° (Found: C, 53·2; H, 6·1; N, 7·3; S, 16·8. $C_{17}H_{22}O_4N_2S_2$ requires C, 53·4; H, 5·8; N, 7·3; S, 16·7%).

Attempts to cyclise *o*-acetylphenyl methanesulphonate (I; R = H) to *2-o*-hydroxyphenylprop-1-ene-1-sulphonic sultone (III; R = H) by using boron trifluoride at 0° or anhydrous glycerol [4] at 270—280° proved unsuccessful.

o-Acetylphenyl benzenesulphonate (from *o*-hydroxyacetophenone, benzenesulphonyl chloride,

[4] Dunne, Gowan, Keane, O'Kelly, O'Sullivan, Roche, Ryan, and Wheeler, *J.*, 1950, 1252.

and pyridine) separated from light petroleum (b. p. 60—80°) in plates, m. p. 71—72° (Found : C, 60·9; H, 4·5; S, 11·7. $C_{14}H_{18}O_4S$ requires C, 60·9; H, 4·4; S, 11·6%).

o-Acetylphenyl toluene-p-sulphonate separated in needles, m. p. 95—96° (Found : C, 62·2; H, 4·9; S, 10·7. $C_{15}H_{14}O_4S$ requires C, 62·1; H, 4·9; S, 11·0%).

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848. *Some 5α : 6α-Epoxy-3-oxo-steroids.*

By Bernard Ellis and Vladimir Petrow.

Some 5α : 6α-epoxy-3-oxo-steroids have been prepared by oxidation of the corresponding 3β-hydroxy-derivatives with chromic acid–pyridine. The method could not be extended to 5β : 6β-epoxy-3β-hydroxy-steroids as the two compounds studied were converted into 6-oxygenated 3-oxo-Δ⁴-steroids.

Certain 5 : 6-epoxy-3-oxo-steroids of the (*allo*)pregnane series were required for biological study. Their direct preparation by epoxidation of the corresponding 3-oxo-Δ⁵-steroids seemed unattractive from earlier studies in the cholesterol series. Thus Ruzicka and Bosshard [1] in 1937 oxidised cholest-5-en-3-one with perbenzoic acid, obtaining two isomeric products regarded as the corresponding 5 : 6-epoxides and arbitrarily assigned the designations "α" and "β." Certain fission reactions of the so-called "β-"epoxide, however, led Urushibara and Chuman [2] in 1949 to reformulate this compound as 5α : 6α-epoxycholestan-3-one. Mori and Mukawa [3] subsequently concluded that the previously designated "α-"epoxide was best represented as an unsaturated lactone. In seeking a more convenient route to the required compounds we studied the oxidation of 3β-hydroxy-5 : 6-epoxides with chromium trioxide–pyridine.[4]

From cholesterol α-epoxide we readily obtained 5α : 6α-epoxycholestan-3-one in moderate yield.* Similar oxidation of 5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one [5] furnished 5α : 6α-epoxy*allo*pregnane-3 : 20-dione, the constitution of which followed from its conversion by hydrogen bromide into 6β-bromo-5α-hydroxy*allo*pregnane-3 : 20-dione, which was dehydrated by thionyl chloride in pyridine to the known 6β-bromoprogesterone.[6] 21-Acetoxy-5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one,[7] obtained in improved yield by oxidation of 21-acetoxy-3β-hydroxypregn-5-en-20-one with monoperphthalic acid, was similarly converted into 21-acetoxy-5α : 6α-epoxy*allo*pregnane-3 : 20-dione.

Oxidation of 5β : 6β-epoxy-3β-hydroxy-steroids with chromium trioxide–pyridine followed a less consistent pattern. Cholesterol 5β : 6β-epoxide gave a product from which only 6β-hydroxycholest-4-en-3-one could be isolated. The hitherto unknown 5β : 6β-epoxy-3β-hydroxypregnan-20-one was obtained together with a smaller quantity of the easily separated 5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one, by treating with methanolic potassium hydroxide the material formed by reacting 3β-hydroxypregn-5-en-20-one with hypobromous acid. Its oxidation gave a complex product which yielded only pregn-4-ene-3 : 6 : 20-trione on chromatography.

Addition of hypobromous acid to the ethylenic linkage of 21-acetoxy-3β-hydroxypregn-5-en-20-one, followed by elimination of hydrogen bromide by heating the material with ethanolic potassium acetate, led to the formation of an apparently homogeneous compound,

* Since completion of this work, our attention has been drawn to a similar preparation of 5α : 6α-epoxycholestan-3-one (Mori and Mukawa, *Proc. Japan Acad.*, 1955, **31**, 532).

[1] Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244.
[2] Urushibara and Chuman, *Bull. Chem. Soc. Japan*, 1949, **22**, 273.
[3] Mori and Mukawa, *ibid.*, 1954, **27**, 479.
[4] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[5] Ehrenstein and Stevens, *J. Org. Chem.*, 1941, **6**, 908; Davis and Petrow, *J.*, 1950, 1185.
[6] Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 4712.
[7] Ehrenstein, *J. Org. Chem.*, 1941, **6**, 626.

$C_{22}H_{34}O_5$, m. p. 192°, initially regarded as 21-acetoxy-5β : 6β-epoxy-3β-hydroxypregnan-20-one. This material was, however, oxidised by chromium trioxide–pyridine to a mixture from which 21-acetoxy-5α : 6α-epoxy*allo*pregnan-20-one was readily isolated, albeit in low yield. The ultraviolet absorption spectra of various mother-liquor fractions showed maxima at 240 and 249 mμ, but the compounds responsible for these absorptions were not obtained pure. These results, together with considerations of molecular-rotation data, led us to suspect the homogeneity of the epoxide, m. p. 192°. Its constitution as the 1 : 1 molecular compound of 21-acetoxy-5β : 6β-epoxy-3β-hydroxypregnan-20-one and the corresponding 5α : 6α-epoxide followed from chromatographic resolution of its diacetate into 3β : 21-diacetoxy-5β : 6β-epoxypregnan-20-one and 3β : 21-diacetoxy-5α : 6α-epoxy-*allo*pregnan-20-one which passed on equimolar admixture into the fully acetylated derivative of the product, m. p. 192°.

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube. The ultraviolet absorption spectrum (in *iso*propyl alcohol) was kindly determined by Mr. M. T. Davies, B.Sc.

5α : 6α-Epoxycholestan-3-one.—Cholesterol 5α : 6α-epoxide (3 g.) in pyridine (30 ml.) was added to chromium trioxide (3 g.) in pyridine (30 ml.). The mixture was kept overnight and then poured into ether (200 ml.), the solution washed with dilute acetic acid, aqueous sodium carbonate, water, and dried, and the solvent removed. Crystallisation of the residue from aqueous ethanol gave 5α : 6α-epoxycholestan-3-one (1·8 g.), needles, m. p. 122—123°, $[\alpha]_D^{20}$ −39° (*c*, 1·0) (Found: C, 81·0; H, 10·8. Calc. for $C_{27}H_{44}O_2$: C, 81·0; H, 11·1%). No depression in m. p. was obtained on admixture with an authentic specimen prepared from cholest-5-en-3-one.

*5α : 6α-Epoxy*allo*pregnane-3 : 20-dione.*—5α : 6α-Epoxy-3β-hydroxy*allo*pregnan-20-one (2 g.) in pyridine (20 ml.) was oxidised with chromium trioxide (2 g.) in pyridine (20 ml.) for 18 hr. and the product isolated as described above. The *epoxide* (1·3 g.) formed prisms (from methylene dichloride–methanol), m. p. 194°, $[\alpha]_D^{21}$ +25° (*c*, 1·03) (Found: C, 76·7; H, 9·1. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·15%).

*6β-Bromo-5α-hydroxy*allo*pregnane-3 : 20-dione.*—The foregoing compound (300 mg.) in acetone (15 ml.) was treated with hydrogen bromide–acetic acid (0·2 ml. of 50% w/w) in acetone (5 ml.). The pure *bromohydrin* (270 mg.) was collected after 10 min.; the crystals had m. p. 165° (decomp.) (Found: C, 61·7; H, 7·8; Br, 19·4. $C_{21}H_{31}O_3Br$ requires C, 61·3; H, 7·6; Br, 19·4%).

6β-Bromoprogesterone.—The foregoing compound (400 mg.) in pyridine (7 ml.) at 0° was treated with thionyl chloride (0·2 ml.) added dropwise during 5 min. After a further 10 min. at 0°, the mixture was poured into ice-water and the solid collected and air-dried giving material (350 mg.), m. p. 140° (decomp.). Purified from acetone–hexane, 6β-bromoprogesterone formed prisms, m. p. 145° (decomp.) (Found: C, 63·9; H, 8·0. Calc. for $C_{21}H_{29}O_2Br$: C, 64·1; H, 7·4%), not depressed on admixture with an authentic specimen.[6]

*21-Acetoxy-5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one.*—21-Acetoxy-3β-hydroxypregn-5-en-20-one (5 g.) in methylene dichloride (30 ml.) was treated with monoperphthalic acid (3·6 g.) in ether (60 ml.) for 3 hr. at room temperature. Thereafter the mixture was diluted with methylene dichloride, washed with dilute alkali and water, and dried, and the solvent removed. The residue was crystallised from acetone, giving 21-acetoxy-5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one (4·1 g.) in needles, m. p. 200—201°, $[\alpha]_D^{22}$ +26° (*c*, 0·97) [Ehrenstein[7] gives m. p. 195—197°, $[\alpha]_D$ +15·6° (in acetone)]. A further quantity (600 mg.) of 5α : 6α-epoxide with m. p. 195—197° was obtained by concentration of the mother-liquor.

*3β : 21-Diacetoxy-5α : 6α-epoxy*allo*pregnan-20-one*, prepared by acetylating the foregoing compound, crystallised from methanol in needles, m. p. 178°, $[\alpha]_D^{21}$ +20° (*c*, 0·93) (Found: C, 69·5; H, 8·4. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

*21-Acetoxy-5α : 6α-epoxy*allo*pregnane-3 : 20-dione.*—21-Acetoxy-5α : 6α-epoxy-3β-hydroxy-*allo*pregnan-20-one (2 g.) was oxidised overnight with chromium trioxide (2 g.) in pyridine (40 ml.) and the product (1·2 g.; m. p. 190—200°) isolated with ether. Purified from aqueous ethanol, the *epoxide* formed needles, m. p. 202—203°, $[\alpha]_D^{22}$ +34° (*c*, 0·78) (Found: C, 71·2; H, 8·6. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

Oxidation of Cholesterol 5β : 6β-Epoxide.—Cholesterol β-epoxide (2 g.) was oxidised as in the foregoing preparation and the product, isolated with ether, triturated with cold light petroleum (10 ml.). The insoluble fraction (700 mg.; m. p. *ca.* 160°) was purified from aqueous methanol to give 6β-hydroxycholest-4-en-3-one, flat needles, m. p. 190—191°, alone or on admixture

with an authentic specimen.[8] Acetylation gave 6β-acetoxycholest-4-en-3-one, m. p. and mixed m. p. 102°.

Crystalline material could not be isolated from the fraction soluble in light petroleum.

5β : 6β-Epoxy-3β-hydroxypregnan-20-one.—3β-Hydroxypregn-5-en-20-one (10 g.), suspended in a mixture of dioxan (200 ml.) and water (50 ml.), was treated with *N*-bromoacetamide (7 g.) followed by perchloric acid (2 ml. of 72%) in water (10 ml.). The mixture was stirred for 6 min.; a clear yellow solution was obtained. After addition of a little aqueous sodium sulphite, the mixture was poured into a large volume of water and extracted twice with ether. The combined extracts were well washed, dried, and concentrated to small bulk to give a sparingly soluble solid [6·5 g.; m. p. *ca.* 140° (decomp.)], which could not be recrystallised satisfactorily. It was heated under reflux for 5 min. with potassium hydroxide (3 g.) in methanol (60 ml.), and the solid obtained on pouring the mixture into water crystallised once from aqueous methanol to give needles (4·2 g.), m. p. 172—176°, $[\alpha]_D^{20}$ +52°. Further crystallisation from ethyl acetate gave 5β : 6β-*epoxy*-3β-*hydroxypregnan*-20-*one* (2·4 g.), needles, m. p. 188—189°, $[\alpha]_D^{23}$ +71° (*c*, 1·04) (Found : C, 75·7; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%). The 3β-*acetate* crystallised from aqueous methanol in blades, m. p. 133—134°, $[\alpha]_D^{20}$ +52° (*c*, 1·06) (Found : C, 73·9; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%).

The ethyl acetate mother-liquor when cooled to below 0° deposited material (0·9 g.; m. p. 170—178°) which, on purification from aqueous ethanol, gave 5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one [8] in plates, m. p. 190—191°, $[\alpha]_D^{20}$ +1° (*c*, 1·01) (Found : C, 75·6; H, 9·5%), identified by conversion into the 3β-acetate,[8] m. p. 167—168°, $[\alpha]_D^{20}$ +7° (*c*, 1·3).

Oxidation of 5β : 6β-Epoxy-3β-hydroxypregnan-20-one.—The epoxide (1·9 g.) was treated overnight with chromium trioxide (2 g.) in pyridine (40 ml.), and the product isolated with ether. Purification by direct crystallisation could not be achieved. The material was therefore acetylated in pyridine at room temperature and chromatographed on alumina (50 g.; B.D.H.). The solid fractions (600 mg.) obtained on elution with benzene–ethanol (98 : 2) were purified from methanol to give needles of pregn-4-ene-3 : 6 : 20-trione, m. p. 193—195°, $[\alpha]_D^{20}$ +29° (*c*, 1·2), $\lambda_{max.}$ 251 mμ (ε 10,100) (Found : C, 76·4; H, 8·8. Calc. for $C_{21}H_{28}O_3$: C, 76·8; H, 8·6%) [Amendolla *et al.*[9] give m. p. 193—194°, $[\alpha]_D$ +30°, $\lambda_{max.}$ 250 mμ (ε 10,600)]. Further elution of the column failed to give crystalline fractions.

(α + β)-Epoxide derived from 21-Acetoxy-3β-hydroxypregn-5-en-20-one.—A solution of 21-acetoxy-3β-hydroxypregn-5-en-20-one (5 g.) in a mixture of dioxan (90 ml.) and water (20 ml.) was treated with *N*-bromoacetamide (3·5 g.), followed by perchloric acid (1 ml. of 72%) in water (5 ml.). After 5 min., a few ml. of aqueous sodium sulphite were added, the mixture was poured into water, and the product was extracted with ether. Concentration of the washed and dried extract gave a solid [4·1 g.; m. p. *ca.* 145° (decomp.)] which failed to crystallise satisfactorily. It was heated under reflux for 20 min. with anhydrous potassium acetate (5 g.) in ethanol (50 ml.), and the solid (3·1 g.; m. p. 177—180°) obtained on pouring the mixture into water was crystallised from aqueous ethanol. The (α + β)-*epoxide* formed needles, m. p. 191—192°, $[\alpha]_D^{23}$ +47° (*c*, 0·78) (Found : C, 70·6; H, 8·4. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). Attempts to resolve the 1 : 1 molecular compound by chromatography were unsuccessful.

The 3β-*acetoxy-derivative* formed plates (from ethanol), m. p. 155—156°, $[\alpha]_D^{20}$ +55° (*c*, 0·84) (Found : C, 69·1; H, 8·5. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). It (1 g.) was chromatographed on alumina (25 g.; B.D.H.) in benzene. Elution with the same solvent gave a solid (450 mg.) which was crystallised from methanol. 3β : 21-*Diacetoxy*-5β : 6β-*epoxypregnan*-20-*one* separated in needles, m. p. 161—162°, $[\alpha]_D^{22}$ +87° (*c*, 0·76) (Found : C, 69·8; H, 8·7%). Further elution of the column with methylene dichloride gave material crystallising from aqueous ethanol in needles, m. p. 176—178°, $[\alpha]_D^{20}$ +24°. This material gave no depression on admixture with an authentic specimen of 3β : 21-diacetoxy-5α : 6α-epoxy*allo*pregnan-20-one.

A mixture of the foregoing β-epoxide (100 mg.), m. p. 161—162°, and α-epoxide (100 mg.), m. p. 178°, was dissolved in hot ethanol (5 ml.). The plates which separated had m. p. 155°, $[\alpha]_D^{20}$ +56°, and consisted of the 1 : 1 molecular compound.

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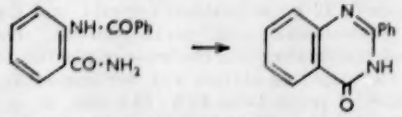
[8] Ellis and Petrow, *J.*, 1939, 1078.
[9] Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226.

849. *Syntheses in the Quinazolone Series. Part IV.* The Conversion of N-Aroylorthanilamides into 2-Arylquinazol-4-ones.*

By Henry Stephen and (the late) George Wadge.

N-Aroylorthanilamides are rapidly converted by aqueous sodium hydroxide into the corresponding 2-arylquinazolones (cf. Körner [1]). An alternative synthesis involves the condensation of *N*-α-chlorobenzylidenetoluene-*p*-sulphonamide with methyl anthranilate and subsequent hydrolysis.

Körner [1] first prepared 2-phenyl-4-quinazolone (II) by the action of aqueous potassium hydroxide on *N*-benzoylorthanilamide (I), and the reaction has now been extended to the synthesis of a number of 2-aryl-4-quinazolones of type (II). Amides of type (I) are obtained from the corresponding methyl *N*-aroylorthanilates, which are readily obtained by aroylation of methyl anthranilate. The conversion of the esters into amides by the action of ammonia at room temperature requires from 14 to 30 days to give good yields. In some instances the amides were partially converted into the corresponding quinazolones by the action of ammonia. The amides are completely converted into quinazolones by heating them with 5% aqueous sodium hydroxide for 15 min. Attempts to reduce the time for the formation of the amides by heating the esters with ammonia resulted in hydrolysis and poor yields of amides.



$$p\text{-}C_6H_4Me\cdot SO_2\cdot N{:}CPh\cdot NH\cdot C_6H_4\cdot CO_2Me + NH_3 + H_2O \longrightarrow (II) + p\text{-}C_6H_4Me\cdot SO_2\cdot NH_2 + MeOH$$

(III)

In preliminary experiments attempts were made to prepare the quinazolones by heating methyl *N*-benzoylanthranilate with ammonium carbonate, but the yield was negligible. A small yield was obtained by heating *N*-benzoylanthranilic acid with ammonium carbonate. A more promising synthesis was the condensation of *N*-α-chlorobenzylidenetoluene-*p*-sulphonamide [2] with methyl anthranilate to give *N*-(*o*-methoxycarbonylphenyl)-*N'*-(toluene-*p*-sulphonyl)benzamidine (III), which on hydrolysis in presence of ammonia gave 2-phenyl-4-quinazolone (92%): this synthesis was not investigated further.

Experimental

Preparation of Methyl N-Aroylanthranilates.—Most of the *esters* in Table 1 were prepared from the acid chloride and methyl anthranilate in presence of sodium acetate in aqueous ethanol (method 1),[3] and the others by aroylation in pyridine (method 2).[4] All the esters formed needles from ethanol.

Preparation of N-Aroylorthanilamides.—The following illustrates the preparation of the *amides* in Table 2. Methyl benzoylorthanilate (44·4 g.) in ethanol (2 l.) was saturated with ammonia at 0°, and then kept at room temperature in a stoppered bottle for 14—30 days. Removal of ethanol gave *N*-benzoylanthranilamide (95%) which crystallised from ethanol in needles, m. p. 218°. The esters (nos. 2—5, 7, 8, 10), on treatment with ammonia, gave mixtures of amides and the corresponding quinazolones and no attempt was made to separate them. Amides in Table 2 and the mixtures were converted into the corresponding quinazolones by boiling them for ½ hr. with 5% aqueous sodium hydroxide. The alkaline solution was filtered into dilute hydrochloric acid, then decolorised (charcoal), and the quinazolone was precipitated on addition of ammonia. All the *quinazolones* in Table 3 crystallised in needles from ethanol or ethanol–acetic acid.

* Part III, *J.*, 1956, 4178.

[1] Körner, *J. prakt. Chem.*, 1887, **36**, 155.
[2] Kemp and Stephen, *J.*, 1948, 110.
[3] Reverdin, *Ber.*, 1909, **42**, 1524.
[4] Dehn and Ball, *J. Amer. Chem. Soc.*, 1914, **36**, 2091.

N-(o-*Methoxycarbonylphenyl*)-N'-(*toluene*-p-*sulphonyl*)*benzamidine* (III).—*N*-Chlorobenzylidenetoluene-*p*-sulphonamide (10·5 g.) in dry acetone (50 c.c.) was added to methylanthranilate (13·5 g.) in dry acetone (50 c.c.). There was a slight rise of temperature and methyl anthranilate hydrochloride was deposited during ½ hr. and then removed. The acetone filtrate was

TABLE 1. *Methyl N-aroylorthanilates.*

No.	Ar	Method	Yield (%)	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
1	PhO·CH_2	1, 2	82	87°	67·3	5·4	$C_{16}H_{15}O_4N$	67·3	5·3
2	o-C_6H_4Me·O·CH_2	2	84	85	68·2	6·0	$C_{17}H_{17}O_4N$	68·2	5·7
3	m-C_6H_4Me·O·CH_2	2	96	88	68·1	5·8			
4	p-C_6H_4Me·O·CH_2	2	90	95	68·1	5·9			
5	Ph·CH_2	1, 2	55	58	71·35	5·8	$C_{16}H_{15}O_2N$	71·36	5·62
6	p-C_6H_4·OMe	1	80	113	67·2	5·3	$C_{16}H_{15}O_4N$	67·36	5·3
7	3 : 4-$C_6H_3(OMe)_2$	1	60	108	64·9	5·25	$C_{17}H_{17}O_5N$	64·95	5·13
8	3 : 4 : 5-$C_6H_2(OMe)_3$	1	60	138	62·54	5·6	$C_{18}H_{19}O_6N$	62·6	5·55
9	o-C_6H_4Me	1	83	114	71·45	5·83	$C_{16}H_{15}O_3N$	71·36	5·62
10	m-C_6H_4Me	1	71	74	71·45	5·59			
11	p-C_6H_4Me	1	40	100	71·35	5·64			
12	Ph·CH:CH	1	73	99	72·5	5·51	$C_{17}H_{15}O_3N$	72·58	5·38

TABLE 2. *N-Aroylorthanilamides.*

Ar	Yield (%)	Time (days)	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Ph	95	30	218°	—	—	—	—	—
PhO·CH_2	80	30	234	66·5	5·17	$C_{15}H_{14}O_3N_2$	66·65	5·22
p-C_6H_4·OMe	25	30	209	66·86	5·25	$C_{15}H_{14}O_3N_2$	66·65	5·22
o-C_6H_4Me	20	30	185	71·12	5·6	$C_{15}H_{14}O_2N_2$	70·85	5·5
p-C_6H_4Me	15	30	218	71·1	5·6	$C_{15}H_{14}O_2N_2$	70·85	5·5
Ph·CH:CH	15	14	237	72·14	5·37	$C_{16}H_{14}O_2N_2$	72·16	5·3

TABLE 3. *2-Substituted quinazolones.*

Ar	Yield (%)	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Ph [a]	90	236°	—	—	—	—	—
PhO·CH_2	91	209	71·56	5·05	$C_{15}H_{12}O_2N_2$	71·4	4·8
o-C_6H_4Me·O·CH_2	80	185	72·27	5·4	$C_{16}H_{14}O_2N_2$	72·16	5·3
m-C_6H_4Me·O·CH_2	90	233	72·19	5·4			
p-C_6H_4Me·O·CH_2	70	235	72·02	5·46			
Ph·CH_2 [b]	75	256	76·28	5·35	$C_{15}H_{12}ON_2$	76·25	5·12
p-C_6H_4·OMe	98	247	71·34	4·9	$C_{16}H_{14}O_2N_2$	71·41	4·8
3 : 4-$C_6H_3(OMe)_2$	90	246	68·21	5·13	$C_{16}H_{14}O_3N_2$	68·06	5·0
3 : 4 : 5-$C_6H_2(OMe)_3$	56	255	65·27	5·31	$C_{17}H_{16}O_4N_2$	65·38	5·16
Ph·CH:CH [c]	90	246	77·28	4·88	$C_{16}H_{12}ON_2$	77·4	4·87
o-C_6H_4Me	89	236	76·2	5·2	$C_{15}H_{12}ON_2$	76·25	5·12
m-C_6H_4Me	63	212	76·13	5·28			
p-C_6H_4Me	80	241	76·23	5·19			

[a] Bogert, Gortner, and Amend (*J. Amer. Chem. Soc.*, 1911, **33**, 949) give m. p. 234° (corr.). [b] Kõnig (*J. prakt. Chem.*, 1904, **69**, 20) gives m. p. 242° and Aggarawal and Ray (*J. Indian Chem. Soc.*, 1929, **6**, 288) give m. p. 247°. [c] Bogert, Beal, and Amend (*J. Amer. Chem. Soc.*, 1910, **32**, 1657) give m. p. 252° (corr.).

steam-distilled to remove unchanged methyl anthranilate, and the residue made alkaline with ammonia, giving needles (13·7 g., 94%), which after recrystallisation from ethanol melted at 146·5° (Found: C, 64·7; H, 5·1. $C_{22}H_{20}O_4N_2S$ requires C, 64·7; H, 4·9%). For conversion into 2-phenyl-4-quinazolone, the amidine (III) (3 g.) was dissolved in ethanol, saturated with ammonia, allowed to remain at room temperature overnight, and poured into water (50 c.c.). 2-Phenyl-4-quinazolone (1·5 g., 92%), m. p. 235°, was obtained (Found: C, 75·6; H, 4·5. Calc. for $C_{14}H_{10}ON_2$: C, 75·7; H, 4·5%). The quinazolone was also obtained by heating an intimate mixture of *N*-benzoylanthranilic acid (5 g.) with ammonium carbonate (5 g.) at 250° for 45 min., and adding small amounts of ammonium carbonate from time to time. The fused mass was cooled, macerated with dilute hydrochloric acid, and filtered. The insoluble portion was *N*-benzoylanthranilic acid, m. p. 178°, which was removed, and the acidic filtrate on addition of ammonia gave 2-phenyl-4-quinazolone, m. p. 235° (2·0 g., 44%).

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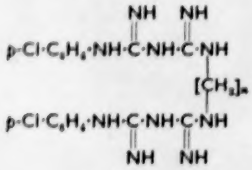
850. *Bisdiguanides having Antibacterial Activity.*

By F. L. Rose and G. Swain.

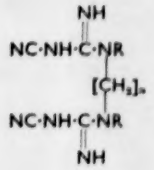
A series of bisdiguanides has been prepared either by condensing one mol. of a biscyanoguanidine with two mols. of an amine hydrochloride, or by the converse interaction of two mols. of an *N*-arylcyanoguanidine with one of a diamine salt. One of the products, 1 : 6-di-(N^5-*p*-chlorophenyl-N^1-diguanido)hexane (chlorohexidine B.P.C.), has found practical use as an antibacterial agent.

The occurrence of antimalarial activity in certain substituted diguanides [1] stimulated the search for other therapeutically useful members of this series, and in due course led to the discovery of high antibacterial activity, more especially amongst a series of bisdiguanides. One such compound, 1 : 6-di-(N^5-*p*-chlorophenyl-N^1-diguanido)hexane (I ; $n = 6$) has recently been introduced into medical and veterinary practice under the common name chlorhexidine B.P.C. ("Hibitane"*).[2] The present communication is concerned with the chemistry of this substance, and also with that of related compounds, many of which were prepared during the investigation of its mode of action.

The original observation of marked bacteriostatic action was made with the mixture of polymeric diguanides that resulted from the fusion of 1 : 6-di-(N^3-cyano-N^1-guanidino)-hexane (II ; R = H, $n = 6$) with hexamethylenediamine dihydrochloride. Attempts to



(I)



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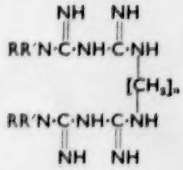

(III)

determine actual chain lengths, or to separate the mixture into homogeneous fractions, were unsuccessful. Since, however, it was known that molecules carrying only one diguanide residue were but weakly antibacterial, it was clearly desirable to determine the degree of molecular complexity necessary for high antimicrobial potency. For this purpose the step-wise synthesis of polydiguanides was undertaken. In the event, full biological activity was reached immediately two diguanide systems were incorporated into each drug molecule, and effort was then concentrated on ascertaining the optimum distance which should exist between these two residues and the most effective types of end groupings—whether, for example, antibacterial activity was highest in bisdiguanides in which the terminal groups were aryl, alkyl, or heterocyclic. In addition it was desired to examine the effect of replacing the diguanide residues by other less complex basic groups such as that of guanidine. The relevant biological findings have already been reported elsewhere ; [3] briefly it was found that highest antibacterial activity occurred in the series (I), and in particular when $n = 5$, 6, or 7. Since hexamethylenediamine was most readily available to us, the majority of the subsequent preparations were based on this substance. The introduction of hydroxyl or carbonyl substituents into the terminal aryl groups almost eliminated antibacterial action, as did the replacement of diguanide by guanidine, while the analogous wholly alkyl-bisdiguanides (III ; R = alkyl, R′ = H or alkyl, $n = 6$) were only fractionally as effective (one-third to one-tenth) as the compound (I).

The standard methods of preparing the bisdiguanides were employed, similar to those developed for the simple antimalarial monodiguanides.[1,4] The first required the reaction

* Registered Trade Mark of Imperial Chemical (Pharmaceuticals) Ltd.

[1] Curd and Rose, *J.*, 1946, 729.
[2] B.P. 705,838.
[3] Davies, Francis, Martin, Rose, and Swain, *Brit. J. Pharmacol.*, 1954, **9**, 192.
[4] Curd, Hendry, Kenny, Murray, and Rose, *J.*, 1948, 1630.

TABLE 1. *Biscyanoguanidines* (II) (R = H except as stated).

−[CH$_2$]$_n$−	Butanol (c.c.)/ 0·01 mol.	Reaction time (hr.)	Solvent for crystn.	M. p.†	Yield (%)	Formula	Found (%) C	H	N	Required (%) C	H	N
[CH$_2$]$_2$	15	12	H$_2$O	248—250° ‡	57	$C_6H_{10}N_8$	36·35	5·3	56·8	37·1	5·15	57·7
[CH$_2$]$_3$	15	16	,,	206 ‡	50—60	$C_7H_{12}N_8$	39·95	5·9	53·5	40·4	5·8	53·5
[CH$_2$]$_4$	14	18	,,	197—199	74	$C_8H_{14}N_8$	43·0	6·9	48·1	43·2	6·3	50·4
[CH$_2$]$_5$	14	20	,,	169—171	58	$C_9H_{16}N_8$	45·2	6·3	46·6	45·8	6·8	47·45
[CH$_2$]$_6$	14	8	,,	202—203 (s 199)	70—80	$C_{10}H_{18}N_8$	47·45	7·45	44·4	48·0	7·2	44·8
[CH$_2$]$_7$	12·5	16	Aq. EtOH	144—146 (s 138—140)	30—40	$C_{11}H_{20}N_8,\frac{1}{2}H_2O$	48·25	7·55	41·25	48·3	7·7	41·0
[CH$_2$]$_{10}$	15	,,	*Aq. EtO·C$_2$H$_4$·OH	184—186 (s 182)	v. low	$C_{14}H_{26}N_8$	54·15	8·0	36·6	54·9	8·5	36·6
[CH$_2$]$_6$ §	15	,,	* Aq. EtOH	186—187	83	$C_{18}H_{34}N_8$	59·3	9·45	30·85	59·7	9·4	30·9
[CH$_2$]$_2$·O·[CH$_2$]$_2$	10	,,	* H$_2$O	138—140 (s 136)	56	$C_{10}H_{18}ON_8$	44·45	6·65	42·3	45·1	6·8	42·1
[CH$_2$]$_2$·O·C$_6$H$_4$(*p*)·O·[CH$_2$]$_2$	15	15	*Aq. EtO·C$_2$H$_4$·OH	204—206	56	$C_{16}H_{22}O_2N_8$	53·25	6·35	30·1	53·6	6·1	31·3
[CH$_2$]$_2$·O·[CH$_2$]$_2$·O·[CH$_2$]$_2$	10	16	Gum used without further purification after removal of salt and solvent.									

* Prisms. † s = sinters. ‡ With decomp. § R = Bu^t.

TABLE 2. *Bis*-p-*chlorophenyldiguanidines* (I).

Code no.	−[CH$_2$]$_n$−	2-Ethoxyethanol (c.c.) per 0·01 mol.	Reaction time (hr.)	Solvent for crystn.	M. p.	Yield (%)	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
20,184	[CH$_2$]$_2$ *	14	6	H$_2$O	245—246° *	26	$C_{18}H_{22}N_{10}Cl_2,2HCl,H_2O$	40·2	5·2	26·3	25·9	40·0	4·8	25·9	26·3
12,483	[CH$_2$]$_3$ ♭	20	4	,,	224—226 *	50	$C_{19}H_{24}N_{10}Cl_2,2HCl,H_2O$	41·4	5·3	24·5	25·2	41·15	5·05	25·3	25·6
12,484	[CH$_2$]$_4$ °	20	3	,,	253—254 *	59	$C_{20}H_{26}N_{10}Cl_2,2HCl$	43·7	5·2	24·6	25·2	43·6	5·1	25·5	25·8
12,485	[CH$_2$]$_5$ ♭	20	6	,,	250	58	$C_{21}H_{28}N_{10}Cl_2,2HCl$	44·4	5·2	24·2	25·5	44·7	5·3	24·8	25·2
10,040	[CH$_2$]$_6$	See text													
12,486	[CH$_2$]$_7$	25	1½	,,	253—254	57	$C_{23}H_{32}N_{10}Cl_2,2HCl$	46·0	5·3	23·7	25·0	46·6	5·7	23·6	24·0
11,383	[CH$_2$]$_{10}$	20	6	Aq. EtOH	246—248	60	$C_{26}H_{38}N_{10}Cl_2,2HCl$	49·25	6·3	21·4	—	49·2	6·3	22·1	—
14,345	[CH$_2$]$_2$·O·[CH$_2$]$_2$	18	2	H$_2$O	236—238	73	$C_{22}H_{30}ON_{10}Cl_2,2HCl$	44·4	5·5	23·3	24·0	44·4	5·4	23·6	24·0
14,411	[CH$_2$]$_2$·O·[CH$_2$]$_2$·O·[CH$_2$]$_2$	20	2½	Aq. COMe$_2$	204—205	50	$C_{24}H_{34}O_2N_{10}Cl_2,2HCl$	46·7	5·4	22·6	22·2	45·1	5·6	22·0	22·3
11,382	[CH$_2$]$_2$·O·C$_6$H$_4$(*p*)·O·[CH$_2$]$_2$	20	9	Aq. EtOH	248—249	35	$C_{28}H_{34}O_2N_{10}Cl_2,2HCl$	49·05	5·2	20·4	—	49·0	5·3	20·4	—
11,384	C$_6$H$_4$(*p*) †	—	—	,,	253—254	70	$C_{22}H_{22}N_{10}Cl_2,2HCl$	46·15	4·35	24·7	—	46·3	4·2	24·6	—
11,385	(*p*)C$_6$H$_4$·CH$_2$·C$_6$H$_4$(*p*) †	—	—	,,	—	50	$C_{29}H_{28}N_{10}Cl_2,2HCl$	52·85	4·6	20·4	—	52·7	4·5	21·2	—

* With decomp. † Method (ii), see text.

TABLE 3. 1 : 6-*Bisdiguanidohexanes* (III; R′ = H, *n* = 6).

Code no.	R	2-Ethoxyethanol (c.c.)/0·01 mol.	Reaction time (hr.)	Solvent	M. p.	Yield (%)	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
10,387	*o*-Ph ♭	16	3	H$_2$O	242—244°	74	$C_{22}H_{32}N_{10},2HCl$	51·55	6·7	27·4	12·9	51·9	6·7	27·5	13·95
10,688	*p*-C$_6$H$_4$Me	25	2	Aq. EtO·C$_2$H$_4$·OH	263—264	90	$C_{24}H_{36}N_{10},2HCl$	53·45	6·5	25·65	—	53·6	7·1	26·1	—
11,108	*p*-C$_6$H$_4$·OH *	,,	2½	EtOH–PrOH	200—202	40	$C_{22}H_{32}O_2N_{10},2HCl$	48·4	6·15	25·3	—	48·8	6·3	25·9	—
10,689	*p*-C$_6$H$_4$·OMe ♭	20	2	MeOH–EtOH	238—240	78	$C_{24}H_{34}O_2N_{10},2HCl$	49·85	6·5	25·5	—	50·6	6·7	24·6	—
10,691	*p*-C$_6$H$_4$·CO$_2$H	25	6	H$_2$O	218—224 *	42	$C_{24}H_{32}O_4N_{10},2HCl$	47·65	6·1	22·7	—	48·2	5·7	23·4	—
10,040	*p*-C$_6$H$_4$Cl °	25	3	,,	260—262	90	$C_{22}H_{30}N_{10}Cl_2,2HCl$	45·5	5·8	24·25	23·8	45·7	5·5	24·2	24·9
11,380	*m*-C$_6$H$_4$Cl	25	9	Aq. EtOH	233—234	10	$C_{22}H_{30}N_{10}Cl_2,2HCl$	46·3	5·95	23·95	—	45·7	4·5	24·2	—
11,386	3 : 4-C$_6$H$_3$Cl$_2$	13	9	EtO·C$_2$H$_4$·OH	259—260	68	$C_{22}H_{28}N_{10}Cl_4,2HCl$	41·2	5·0	21·5	—	40·8	4·6	21·6	—
11,381	2 : 5-C$_6$H$_3$Cl$_2$ ♭	25	8	Aq. EtOH	249—250	34	$C_{22}H_{28}N_{10}Cl_4,2HCl$	40·6	5·2	20·9	—	40·8	4·6	21·6	—
11,110	α-C$_{10}$H$_7$	,,	8	Aq. AcOH	257—258	48	$C_{30}H_{36}N_{10},2HCl$	58·9	6·1	22·7	—	59·1	5·9	23·0	—
10,388	β-C$_{10}$H$_7$ ♭	,,	3	H$_2$O	252—254	74	$C_{30}H_{36}N_{10},2HCl$	59·5	6·2	23·1	10·9	59·1	5·9	23·0	11·7

* Prisms. ♭ Needles. ° Plates. * With decomp.

in nitrobenzene of an *N*-phenylcyanoguanidine with each of the amino-groups of a diamine, and the second, more generally used, was the complementary process in which the biscyanoguanidine (II) interacted with two molecular proportions of the amine NHRR′ (see III), preferably in boiling 2-ethoxyethanol. The biscyanoguanidines were themselves readily accessible from the reaction of the appropriate diamine dihydrochloride with two molecular proportions of sodium dicyanimide in boiling butanol. The yield of the crystallised products was 50—80%, that of the hexamethylene derivative being in the upper range. The intermediate preparations also included examples in which the nitrogen atoms adjacent to the polymethylene chain carried an alkyl group (II; R = alkyl), and others in which ether-oxygen atoms, and in one case additionally a *p*-substituted phenyl residue, were interposed in the polymethylene chain (see Table 1).

A slightly modified procedure was employed for the production of the bisdiguanides (III; R and/or R′ = alkyl) in that a solvent was not required, and the usual practice was to fuse an intimate mixture of the biscyanoguanidines with the alkylamine hydrochlorides at bath temperatures in the range 150—160°. Two bisdiguanides were also made in which the terminal groups were derived from 8-amino-6-methoxyquinoline and 2 : 5-diamino-4 : 6-dimethylpyrimidine severally: in these instances, 2-ethoxyethanol was used as solvent. Finally, the bisguanidine corresponding to the bisdiguanide (I; $n = 6$) was prepared from the related thiourea, itself formed by the interaction of hexamethylene di*iso*thiocyanate with *p*-chloroaniline in boiling ethanol. Amination was effected by alcoholic ammonia in the presence of mercuric oxide.

Experimental

General Method of Preparation of Biscyanoguanidines.—The diamine dihydrochloride (1·0 mol.) and sodium dicyanimide (2·0 mols.) were powdered together, mixed with butanol, and stirred and heated under reflux (bath-temp. 130—140°) for 8—16 hr. After cooling, either the insoluble solid was filtered off and washed with cold water to remove sodium chloride, or, where the product remained in solution, the sodium chloride was first filtered off and the filtrate was then evaporated to dryness under reduced pressure. Details of the experiments are given in Table 1.

1 : 6-*Di*-(N⁵-p-*chlorophenyl*-N¹-*diguanido*)*hexane Dihydrochloride* (10,040).—(i) 1 : 6-Di-(*N*⁵-cyano-*N*¹-guanidino)hexane (30 g., 0·12 mol.), *p*-chloroaniline hydrochloride (39·6 g., 0·12 mol.), and 2-ethoxyethanol (300 c.c.) were stirred together under reflux (bath-temp. 130—140°) for 3 hr. After cooling, the microcrystalline *dihydrochloride* [62 g., 90%; m. p. 260—262° (decomp.)] was filtered off and washed with ethanol. Recrystallisation from water, in which it is sparingly soluble, gave plates, m. p. unchanged (Found: C, 45·5; H, 5·8; N, 24·25; Cl, 23·8. $C_{22}H_{30}N_{10}Cl_2,2HCl$ requires C, 45·7; H, 5·5; N, 24·2; Cl, 24·9%). The *base* could be obtained sensibly free from the hydrochloride only by adding a solution of the latter in hot water to an excess of aqueous sodium hydroxide, and not by the reverse procedure. It formed colourless needles (from methanol), m. p. 133·5—134° (corr.) (Found: C, 52·1; H, 6·0; N, 27·7. $C_{22}H_{30}N_{10}Cl_2$ requires C, 52·3; H, 5·9; N, 27·7%). The *diacetate* crystallised on cooling from a solution of the base in hot dilute acetic acid and after recrystallisation from water formed prisms, m. p. 154—155° (corr.) (Found: C, 48·6; H, 6·4; N, 21·7; loss at 120° *in vacuo*, 3. $C_{22}H_{30}N_{10}Cl_2,2C_2H_4O_2,H_2O$ requires C, 48·5; H, 6·2; N, 21·75; H_2O, 2·8%).

(ii) *N*⁵-*p*-Chlorophenyl-*N*¹-cyanoguanidine (19·5 g., 0·1 mol.), hexamethylenediamine dihydrochloride (10·4 g., 0·11 mol.), and nitrobenzene (50 c.c.) were stirred together at 140—145° (bath-temp.) for 16 hr. The suspension was filtered hot and the well-pressed filter cake was suspended in ethanol and stirred for 1½ hr. Refiltration gave the crude dihydrochloride (15·3 g., 53%; m. p. 257—258°). Substitution of methyl*cyclo*hexanol for nitrobenzene gave only a 20% yield.

All the bis-*p*-chlorophenyldiguanides listed in Tables 2 and 3, with two exceptions, were prepared by method (i). The two exceptions, 11,384 and 11,385 (Table 2), were prepared by method (ii).

Miscellaneous Bisdiguanides.—**1 : 6-*Di*-(N⁵-n-*butyl*-N¹-*diguanido*)*hexane dihydrochloride* (9458).** 1 : 6-Di-(*N*⁵-cyano-*N*¹-guanidino)hexane (1·25 g., 0·055 mol.) and *n*-butylamine hydrochloride (1·1 g., 0·01 mol.) were powdered together and heated at 150—155° for 2 hr. The clear melt solidified after 1½ hr., and the *product* was obtained as a microcrystalline solid

(1·4 g., 59·6%; m. p. 223—224° with sintering at 190—192°) by addition of ethyl acetate to a solution in ethyl alcohol (Found: C, 45·5; H, 8·55; N, 29·55; Cl, 15·15. $C_{18}H_{40}N_{10}.2HCl$ requires C, 46·1; H, 8·95; N, 29·85; Cl, 15·1%). The salt was freely soluble in water.

1 : 6-*Di*-(N⁵-iso*propyl*-N¹-*diguanido*)*hexane dihydrochloride* (9357). 1 : 6-Di-(*N*³-cyano-*N*¹-guanidino)hexane (1·25 g., 0·005 mol.) and *iso*propylamine hydrochloride (0·9 g., 0·01 mol.) were intimately mixed and heated together at 160° for ½ hr. Similarly crystallised from alcohol–ethyl acetate, the microcrystalline *dihydrochloride* (1·1 g., 50%) had m. p. 256—257° (decomp.) (Found: C, 43·3; H, 8·3; N, 32·3. $C_{16}H_{36}N_{10}.2HCl$ requires C, 43·5; H, 8·6; N, 31·75%) and was freely soluble in water.

1 : 6-*Di*-(N⁵-cyclo*hexyl*-N¹-*diguanido*)*hexane dihydrochloride* (9382). 1 : 6-Di-(*N*³-cyano-*N*¹-guanidino)hexane (1·25 g., 0·005 mol.) and *cyclo*hexylamine hydrochloride (1·35 g., 0·01 mol.) were intimately mixed and heated at 160° for 1 hr. Similarly recrystallised from alcohol–ethyl acetate, the *dihydrochloride* had m. p. 234—236° after sintering at 225—230° (Found: N, 26·25. $C_{22}H_{44}N_{10}.2HCl$ requires N, 26·9%).

1 : 6-*Di*-(N⁵N⁵-*pentamethylene*-N¹-*diguanido*)*hexane dihydrochloride* (9383). 1 : 6-Di-(*N*³-cyano-*N*¹-guanidino)hexane (1·25 g., 0·005 mol.) and piperidine hydrochloride (1·2 g., 0·01 mol.) were intimately mixed and heated at 150° for 1½ hr. The originally clear melt solidified after 1 hr. Similarly recrystallised from ethanol–ethyl acetate, the *dihydrochloride* formed prisms, m. p. 231° (1·1 g., 45%) (Found: N, 28·6. $C_{20}H_{40}N_{10}.2HCl$ requires N, 28·4%).

1 : 6-*Di*-[N⁵-(2-*amino*-4 : 6-*dimethylpyrimidin*-5-*yl*)-N¹-*diguanido*]*hexane disulphate* (10,160). 2-Amino-4 : 6-dimethylpyrimidine (5·6 g., 0·04 mol.) was dissolved in 2-ethoxyethanol (50 c.c.) and 1 : 6-di-(*N*³-cyano-*N*¹-guanidino)hexane (5·0 g., 0·02 mol.) added to the stirred solution, followed by ethanolic hydrochloric acid (4·8N; 8·5 c.c., 2 equivs.). The mixture was stirred under reflux for 68 hr., the 2-ethoxyethanol removed under reduced pressure, and the residue dissolved in water (50 c.c.). The brown gum precipitated by addition of 10N-sodium hydroxide was washed by decantation with water and redissolved in dilute hydrochloric acid; the solution was made alkaline with ammonia and filtered (charcoal), and the base reprecipitated with sodium hydroxide solution. After being further washed with water by decantation, the still gummy base was converted into the *disulphate* (7 g.) by adding successively sulphuric acid (*d* 1·84; 3 c.c.) and diethylamine to alkalinity, to its solution in 1 : 1 aqueous ethanol (100 c.c.), filtering (charcoal), and finally adding excess of dry ethanol. Recrystallisation from water afforded prisms (1·8 g.), m. p. 220—225° (decomp.) (Found: C, 35·05; H, 6·4; N, 29·15; S, 8·2. $C_{22}H_{38}N_{14}.2H_2SO_4.2H_2O$ requires C, 34·8; H, 6·1; N, 29·5; S, 8·4%).

1 : 6-*Di*-[N⁵-(6-*methoxyquinolin*-8-*yl*)-N¹-*diguanido*]*hexane dihydrochloride* (10,690). 8-Amino-6-methoxyquinoline (7·0 g., 0·04 mol.), 1 : 6-di-(*N*³-cyano-*N*¹-guanidino)hexane (5·0 g., 0·02 mol.), 2-ethoxyethanol (50 c.c.), and ethanolic hydrochloric acid (6·2N; 6·5 c.c., 2 equivs.) were stirred together under reflux for 3 hr. The orange-coloured suspension slowly dissolved to a clear solution, which finally deposited crystals of the *dihydrochloride* (5·1 g., 45%; m. p. 246—248°). This recrystallised from water in colourless felted needles, m. p. 246—248° (Found: C, 53·2; H, 5·95; N, 24·8. $C_{30}H_{38}O_2N_{12}.2HCl$ requires C, 53·65; H, 5·95; N, 25·0%).

1 : 6-*Di*-(N³-p-*chlorophenyl*-N¹-*thioureido*)*hexane* (11,368). A mixture of hexamethylene di*iso*thiocyanate (10·0 g., 0·05 mol.), *p*-chloroaniline (13·0 g., 0·05 mol.), and ethanol (150 c.c.) was refluxed for 16 hr. and water was then added to crystallisation point. Cooling gave the crude *thiourea* (16 g.) which recrystallised from ethanol in colourless needles (13·8 g., 60%; m. p. 171—172°) (Found: C, 53·1; H, 5·25; N, 12·55. $C_{20}H_{24}N_4S_2Cl_2$ requires C, 52·75; H, 5·3; N, 12·3%).

1 : 6-*Di*-(N³-p-*chlorophenyl*-N³-*guanido*)*hexane* (11,717). Ammonia in ethanol (5·6N; 150 c.c.), followed by mercuric oxide (4·5 g.), was added to a cooled solution of the above thiourea (9·1 g.) in 2-ethoxyethanol (80 c.c.). The suspension was kept at 30—35° for 40 hr., then warmed to 60° and filtered. The bulk of the solvent was distilled under reduced pressure and the *guanidine* (3·5 g.; m. p. 146—147°) was precipitated by slow addition of water. It crystallised from ethanol–water in colourless needles (2·6 g.; m. p. 160—161°) (Found: C, 57·0; H, 6·25; N, 19·8. $C_{20}H_{24}N_8Cl_2$ requires C, 57·0; H, 6·2; N, 19·95%).

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851. *The Synthesis of α- and β-Phenyladipic Acid.*

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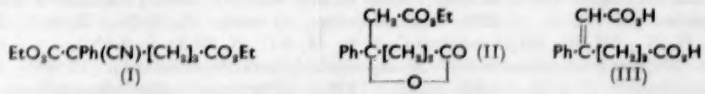
Syntheses are described of α- and β-phenyladipic acid in yields which are greatly superior to those previously reported.

Several methods of preparing α- and β-phenyladipic acid have been described but where the yields are based on readily available materials they are below 10% overall. For example, Case [1] obtained α-phenyladipic acid in about 6% yield from propane-1 : 3-diol and ethyl phenylmalonate. Baker and Jones [2] synthesized this acid from ethyl α-cyano-α-phenylacetate and 3-chloropropyl cyanide in 39% yield, but as the chlorocyanide is prepared from propane-1 : 3-diol in 25% yield,[3] the overall value from readily available compounds is 10%. It is impossible to estimate the yield in Kuhn and Michel's synthesis [4] because the essential information is not given for each of the six stages. Oxidation of 3-phenyl*cyclo*hexene with potassium permanganate to α-phenyladipic acid has been described [5] but the percentage conversion is not recorded.

The need for several hundred grams of each acid in these Laboratories stimulated a search for alternative and better syntheses. The following synthesis, from commercially available starting materials, proved satisfactory and gave consistently good yields of α-phenyladipic acid. Treatment of γ-butyrolactone with hydrogen bromide followed by thionyl chloride and ethanol gave ethyl γ-bromobutyrate.[6] This was condensed with ethyl α-cyano-α-phenylacetate in the presence of sodium ethoxide to yield ethyl α-cyano-α-phenyladipate (I) which was simultaneously hydrolysed and decarboxylated to α-phenyladipic acid (cf. Baker and Jones [2]). The overall yield from γ-butyrolactone was 61%. Ethyl α-cyano-α-phenylacetate was prepared by Wideqvist's method [7] since higher and more consistent yields were obtained than by Horning and Finelli's procedure.[8]



β-Phenyladipic acid was first synthesised (in 8% yield) by Manske [9] from ethyl phenylsuccinate. Von Braun and Weissbach's synthesis [10] from 4-hydroxydiphenyl followed in the same year, but yields are not given for all the steps. A more recent synthesis in 10% yield is that by Price and Karabinos [11] from 2-hydroxydiphenyl by a series of reductions and oxidations. The synthesis of β-2-naphthyladipic acid by Bachmann and Morin [12] furnished a method which, if it could be adapted to the benzene series, promised to be superior. Friedel–Crafts acylation of benzene with succinic anhydride [13] followed by esterification gave ethyl β-benzoylpropionate.[14] The latter was treated with ethyl bromoacetate and zinc dust to produce the lactone (II). Ring opening and hydrolysis of this with aqueous-methanolic sodium hydroxide and hydrogenation of the resulting syrup gave β-phenyladipic acid. The overall yield from succinic anhydride was 42%. A lower yield

[1] Case, *J. Amer. Chem. Soc.*, 1933, **55**, 2927.
[2] Baker and Jones, *J.*, 1951, 787.
[3] Allen, *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 156.
[4] Kuhn and Michel, *Ber.*, 1938, **71**, 1119.
[5] Berlande, *Bull. Soc. chim. France*, 1942, **9**, 641.
[6] Avison and Morrison, *J.*, 1950, 1471.
[7] Wideqvist, *Arkiv Kemi, Mineralog., Geol.*, 1947, **24**, *B*, No. 14.
[8] Horning and Finelli, *Org. Synth.*, 1950, **30**, 43.
[9] Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1104.
[10] Von Braun and Weissbach, *Ber.*, 1931, **64**, 1785.
[11] Price and Karabinos, *J. Amer. Chem. Soc.*, 1940, **62**, 1159.
[12] Bachmann and Morin, *ibid.*, 1944, **66**, 553.
[13] Somerville and Allen, *Org. Synth.*, Coll. Vol. II, p. 81.
[14] Kugel, *Annalen*, 1897, **299**, 50; Adkins and Scanley, *J. Amer. Chem. Soc.*, 1951, **73**, 2854.

of β-phenyladipic acid was obtained when crystalline αβ-dihydro-γ-phenylmuconic acid (III) was isolated from the syrup and subsequently hydrogenated to β-phenyladipic acid.[15]

Experimental

Ethyl γ-Bromobutyrate.—γ-Butyrolactone (64·5 g.) was dissolved in aqueous hydrobromic acid (*d* 1·47; 90 ml.), cooled to 0°, and saturated with hydrogen bromide. Saturation took much less time than if the lactone was dissolved in water.[6] Ethyl γ-bromobutyrate (110·3 g., 75%) b. p. 77—80°/6 mm., n_D^{20} 1·4520, was isolated as described.[6]

Ethyl α-Cyano-α-phenylacetate.—This compound, b. p. 135°/3·5 mm., n_D^{20} 1·5040, was prepared as described by Wideqvist,[7] in 86% yield.

Ethyl α-Cyano-α-phenyladipate [16] (I).—A solution of sodium (10·6 g.) in dry ethanol (170 ml.) was placed in a 1 l. flask fitted with a reflux condenser carrying a drying tube. Ethyl cyanophenylacetate (92·8 g.) was added, followed by ethyl γ-bromobutyrate (87·3 g.). The mixture was refluxed for 6 hr. during which sodium bromide separated. Ethanol was distilled off and water (150 ml.) was added. Ether extracts of this solution were combined and dried and the solvent was removed. Distillation of the residue gave ethyl α-cyano-α-phenyladipate (116·0 g., 85%), b. p. 140—146°/0·02 mm., n_D^{20} 1·4948, as an almost colourless oil.

α-Phenyladipic Acid.—The above ester (120 g.) was refluxed for 27 hr. with concentrated hydrochloric acid (600 ml.). The crystals which separated on cooling were filtered off and washed with cold water. Recrystallisation from water gave α-phenyladipic acid (85·0 g., 96%), m. p. 137° (Found: C, 65·1; H, 6·5. Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·3%). Baker and Jones [8] give m. p. 137—138°.

γ-Oxo-γ-phenylbutyric Acid.—In order to minimise the tendency for the reactants to form a pasty mass, Somerville and Allen's method [13] was modified in that succinic anhydride and aluminium chloride were added in small amounts to the stirred benzene during 1 hr. Isolation of the acid in 92% yield was carried out in the usual way.

Ethyl γ-Oxo-γ-phenylbutyrate.—The acid was esterified by refluxing ethanol and concentrated sulphuric acid for 6 hr. The excess of ethanol was distilled off and the residual oil was taken up in ether. Sulphuric acid was removed by washing with dilute sodium carbonate solution and with water, and the ethereal solution was dried ($MgSO_4$). Removal of the solvent and distillation of the residue gave an 89% yield of the ester, b. p. 120°/0·2 mm., n_D^{20} 1·5196.

γ-Ethoxycarbonylmethyl-γ-phenyl-γ-butyrolactone (II).—To purified zinc powder (8·2 g.), suspended in dry benzene (20 ml.), stirred and heated under reflux, was added dropwise during 5 min. a mixture of ethyl γ-oxo-γ-phenylbutyrate (21·4 g.) and ethyl bromoacetate (20·8 g.). Heating was discontinued where necessary to keep the reaction under control. The greenish-brown mixture was heated under reflux for 50 min., cooled, diluted with benzene, and poured into 20% sulphuric acid (100 ml.). The benzene layer was separated, then washed with aqueous sodium carbonate solution, and with water. After drying and removal of the solvent, distillation gave the *lactone ester* (20·7 g., 80%), b. p. 96—98°/0·1 mm., n_D^{20} 1·5144 (Found: C, 68·7; H, 6·8. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%).

αβ-Dihydro-γ-phenylmuconic Acid.—The above lactone (15·3 g.) was heated under reflux for 4·5 hr. in methanol (200 ml.) and water (80 ml.) containing sodium hydroxide (4·8 g.). Methanol was then distilled off and the solution was acidified. The brown oil which separated was extracted with ether, and the solution dried ($MgSO_4$) and concentrated. Colourless crystals separated after 2 days. Recrystallisation from benzene gave *αβ-dihydro-γ-phenylmuconic acid* (4·7 g., 35%), m. p. 144° (Found: C, 65·5; H, 5·7. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

β-Phenyladipic Acid.—(a) *From γ-ethoxycarbonylmethyl-γ phenyl-γ-butyrolactone.* The lactone (27·4 g.) was heated under reflux for 4·5 hr. with N-sodium hydroxide (219 ml.) and methanol (285 ml.). After evaporation of the methanol and acidification, the mixture was extracted with ethyl acetate. The combined extracts were shaken in an atmosphere of hydrogen in the presence of 5% platinum–charcoal (1·5 g.) until the uptake of hydrogen ceased. After filtration the solvent was allowed to evaporate slowly, whereupon crystals of β-phenyladipic acid (17·0 g., 69%), m. p. 130—135°, were obtained. Recrystallisation from ethyl acetate–benzene gave crystals (16·0 g., 65%), m. p. 146—147° (Found: C, 64·4; H, 6·4. Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·3%).

(b) *From αβ-dihydro-γ-phenylmuconic acid* (III). A solution of αβ-dihydro-γ-phenylmuconic

[15] Cf. Dreiding and Tomasewski, *J. Amer. Chem. Soc.*, 1954, **76**, 540.
[16] Wideqvist, *Arkiv Kemi*, 1951, **3**, No. 7, p. 59.

acid (5·0 g.) in ethyl acetate (100 ml.) was shaken with 10% platinum–charcoal (1 g.) in hydrogen. When hydrogen uptake ceased the catalyst was filtered off and the solvent allowed to evaporate slowly, yielding crystals of β-phenyladipic acid (4·6 g., 91%), m. p. 148°. Price and Karabinos [11] give m. p. 147—148°.

The authors thank Mr. J. E. Lodge for assistance with the experimental work, and British Nylon Spinners Limited for permission to publish these results.

RESEARCH DEPARTMENT, BRITISH NYLON SPINNERS LIMITED,
PONTYPOOL, MONMOUTHSHIRE. [*Received, June 29th*, 1956.]

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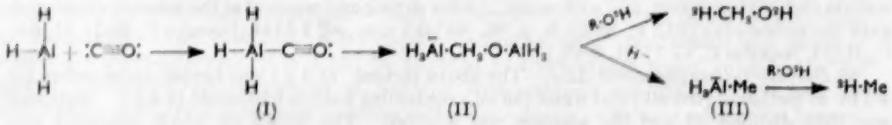
852. *The Reduction of Carbon Monoxide by Lithium Aluminium Hydride.*

By J. F. MARTIN, A. J. NEALE, and H. S. TURNER.

The reduction of carbon monoxide by lithium aluminium hydride has been studied with the aid of deuterium and carbon-14.

CONTRARY to earlier reports,[1] carbon monoxide is absorbed by solutions of lithium aluminium hydride to form a complex which gives methanol and methane on alcoholysis.[2] In preliminary experiments it was never possible to account for more than about 92% of the carbon monoxide absorbed but it was not clear whether the techniques of isolation were at fault or whether there were other minor products. The reaction was therefore examined by using [^{14}C]carbon monoxide, and the yield of methanol and the presence or absence of by-products established by dilution analysis. In this way a satisfactory balance of total carbon and total isotope was obtained (Table 1). About 99·5% of the isotope appeared in methanol and in the gaseous product of the alcoholysis, and there was no evidence of the formation of any other compound from carbon monoxide.

The lithium aluminium hydride reduction of carbon dioxide [2] differs from that of carbon monoxide in that the rate of reaction in comparable conditions is much greater and there is no formation of methane or carbon monoxide. The reduction of carbon dioxide appears to proceed by way of intermediates derived from formate and formaldehyde, both of which are always present in the products of this reaction but are absent from those from carbon monoxide. The following reaction scheme is suggested.[2a] The first step is the co-ordination of carbon monoxide with aluminium hydride (existing in equilibrium with aluminohydride ion) to give a carbonyl hydride (I), the carbonyl group of which undergoes



reduction in the usual manner to give compound (II) which is susceptible to further attack by hydride or aluminohydride ion at the C–O bond to form the methylaluminium compound (III); on alcoholysis (II) yields methanol and (III) methane. Carbon monoxide is much less soluble in organic solvents than carbon dioxide and this, or a low rate of reaction in the co-ordination stage, may be the cause of the slower reaction observed in this case. It will be seen that the formation of the intermediate (II) from carbon monoxide requires two, and of the methylaluminium compound (III) three hydrogen atoms per molecule, and from the relative proportions of methanol and methane in the product the theoretical requirement of hydride is easily calculated. In Run 2 (Table 2) a consumption of 7·75 mmoles was expected, in good agreement with the observed value of 8·14. The intermediate (II) will clearly exist mainly in this simple form only in the earlier stages of the reaction, and when

[1] Brown, Finholt, Nystrom, and Schlesinger, Abs. 110th Amer. Chem. Soc. Meeting, 1946, 27P.
[2] Cox, Turner, and Warne, *J.*, 1950, 3167.
[2a] Cf. Paddock, *Chem. and Ind.*, 1953, 63.

more than one molecule of carbon monoxide has been absorbed for each two molecules of hydride every additional molecule of monoxide reacting will link two molecules of (II). The molecular size will of course be diminished by the reaction leading to the methylaluminium compound. In a typical experiment the solution became turbid at about 0·6 mol. of carbon monoxide per mol. of hydride and by the time 1·2 mol. per mol. had been absorbed a large amount of white solid had separated. As would be expected the yield of methane increased with the ratio of hydride to carbon monoxide, and with increase in time and temperature.

Confirmation of the structures of (II) and (III) was obtained by means of tracer experiments with deuterium, for on decomposing the reaction complex with tetrahydrofurfuryl [^{2}H]alcohol, [$^2H_1$]methane and [^{2}H]methan[^{2}H]ol were formed. No methane was obtained having more than one deuterium atom; this confirms the presence of an unsubstituted methyl group in the intermediate (III).

TABLE 1. *Run* 2.

	Carbon (mg. atoms)	Specific activity (c per mg.-atom of carbon)	Total activity (c)
CO reacting ...	12·60	$1·39 \times 10^{-7}$ [a]	$17·5 \times 10^{-7}$
Gaseous product	6·12 [b]	$1·32 \times 10^{-7}$	$8·07 \times 10^{-7}$
MeOH	6·57 [c]	$1·39 \times 10^{-7}$ [d]	$9·15 \times 10^{-7}$
Residual MeOH (R_1)	0·0025 [c]	$1·39 \times 10^{-7}$ [d]	$0·0035 \times 10^{-7}$
Activity in R_2...	0·06 [c]	$1·39 \times 10^{-7}$ [d]	$0·08 \times 10^{-7}$
Total products	12·75	—	$17·3 \times 10^{-7}$
Discrepancy ...	+ 0·15 (1·2%)	—	$-0·2 \times 10^{-7}$ (1·1%)

[a] Mean of specific activity at beginning and at the end of the experiment. [b] From the analysis and total quantity of mixed gases, assuming that unsaturated hydrocarbons had four carbon atoms. [c, d] Values marked *d* are assumed to be the same as that marked *a*; values marked *c* are calculated on this assumption.

TABLE 2. *Stoicheiometry of the reaction* (*Run* 2).

	mmoles	mmoles
$LiAlH_4$ taken	12·83	—
H_2 in gaseous product	18·75	—
Hydride consumed ...	—	8·14
CO absorbed	—	12·60
Total C in gaseous product (as CO_2) ...	6·12	—
C_nH_{2n+2} (n = 1·02) ...	5·84	—
Methane	—	5·73 [a]
Methanol	—	6·57
Hydride required (calc.)	—	7·75

[a] Minimum value, the saturated hydrocarbon contaminant in the methane being assumed to be ethane.

EXPERIMENTAL

Specific activities are expressed in curies per mg.-atom of carbon and total activities in curies.

Materials.—Tetrahydrofurfuryl alcohol was purified by fractional distillation, the fraction of b. p. 80°/21 mm. being used. Tetrahydrofurfuryl [^{2}H]alcohol was prepared by mixing 99·7% deuterium oxide (2·31 g., 115 mmoles) with tetrahydrofurfuryl alcohol (21·35 g., 209 mmoles). After being kept overnight, the water was removed by azeotropic distillation with benzene (*ca.* 40 g.) in a Dean and Stark apparatus. The benzene was distilled off and the residual alcohol allowed to undergo exchange a second time with deuterium oxide (3·00 g., 150 mmoles). The water was removed as before, and on distillation tetrahydrofurfuryl [^{2}H]alcohol (13·0 g.) was collected at 78—80°/21—23 mm. On the assumption that equilibrium was reached at both stages with no isotope effect, and that the excess of water was completely removed after the first stage without the loss of any alcohol, a deuterium content of *ca.* 80 atoms % was expected in the hydroxyl group; the actual value was 76% (see below). Tetrahydro(tetrahydrofurfuryloxy)pyran, b. p. 135°/25 mm., was prepared as described by Cox, Turner, and Warne.[3]

Lithium aluminium hydride solution was prepared by stirring the coarsely crushed material with tetrahydrotetrahydrofurfuryloxypyran in a carefully dried apparatus. The solution was filtered with the aid of Celite 545 into a flask (Fig. 1) from which it could be dispensed without coming into contact with air. All operations were carried out in dry oxygen-free nitrogen.

Analyses.—Lithium aluminium hydride solutions were estimated by decomposition with excess of tetrahydrofurfuryl alcohol in a simple gas-volumetric apparatus. The results were reproducible to about 0·2%. Felkin's [3] iodimetric method was not applicable to the estimation of lithium aluminium hydride in the presence of tetrahydro(tetrahydrofurfuryloxy)pyran.

All deuterium analyses were carried out in the mass spectrometer. Methane and methanol

[3] Felkin, *Bull. Soc. chim. France*, 1951, 347.

were introduced directly. Deuterium in the hydroxyl group of tetrahydrofurfuryl alcohol was determined as methane after reaction with an excess of methylmagnesium iodide in *n*-butyl ether.

As samples of deuteromethanols were not available for standardising the mass spectrometer, it was assumed that the sensitivities for the deuterated compounds were the same as for methanol. In the case of the methane analyses, the spectrum of pure methane obtained on our instrument was very similar to that published for methane and consequently it was considered justifiable to use published data for the mass spectrum of monodeuteromethane in our calculations. The isotopic composition of the methanol was calculated from the ratios of the peaks at m/e 32 and 34 and at m/e 33 and 34. The analyses of methane and monodeuteromethane mixtures were obtained from the peak heights at m/e = 15, 16, and 17. Accurate quantitative analyses were not required for the purpose of determining the course of the reactions and any errors introduced by the above assumptions would not affect our proposals for the mechanisms.

Samples were burned and counted for ^{14}C as described by Turner and Warne.[4]

FIG. 1.

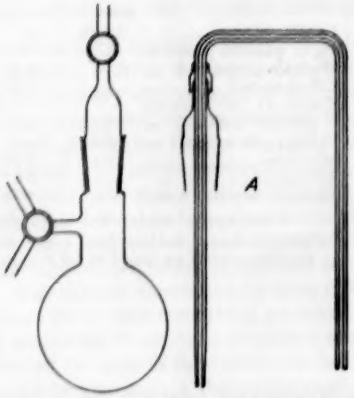
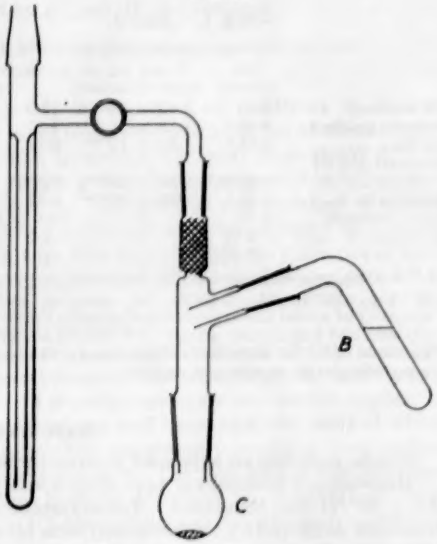


FIG. 2.



Apparatus.—A vacuum manifold of small volume, generally similar to that described by Cox and Turner (Fig. 1),[5] was connected through a Töpler pump to a calibrated storage bulb fitted with a manometer. The reactions were carried out in vessels attached to the manifold.

Preparation of [^{14}C]*Carbon Monoxide.*—The apparatus in Fig. 2 was connected to the manifold through a second trap (not shown). The side-tube *B* contained outgassed 100% sulphuric acid (*ca.* 10 ml.) which could be tipped by rotation about the joint on sodium [^{14}C]formate (15—25 mmoles) in flask *C*. The first trap was cooled by solid carbon dioxide and the second by liquid nitrogen. After thorough evacuation of the apparatus the acid was added to the formate and the carbon monoxide evolved was pumped into the storage bulb. The reaction took place readily in the cold and the yield of carbon monoxide was almost quantitative.

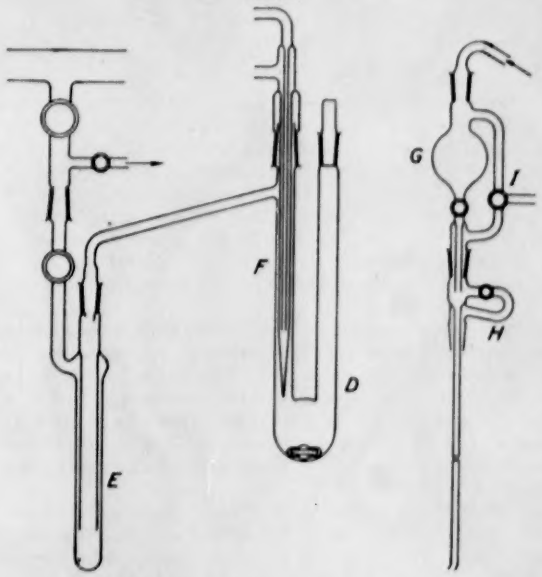
Reaction of Carbon Monoxide with Lithium Aluminium Hydride.—(i) *General.* Lithium aluminium hydride solution (*ca.* 14 g. of a solution containing 0·877 mmole of hydride per g.) was blown under nitrogen pressure through the siphon *A* against a countercurrent of nitrogen into flask *D* (Fig. 3) which had been baked for several hours at 120°. The quantity was determined by weighing before and after delivery. The flask was attached to the trap *E* and thoroughly evacuated while the hydride solution was stirred at room temperature. Stirring was effected by a magnetically operated stainless iron capsule which allowed thorough emulsification of gas and liquid. The stirring was interrupted while carbon monoxide was pumped into the

[4] Turner and Warne, *J.*, 1953, 789.
[5] Cox and Turner, *J.*, 1950, 3176.

flask and manifold from the storage bulb to give a pressure of about one atmosphere; there was no detectable reaction during the addition. The solution was then stirred vigorously and heated rapidly to 55—60° whereupon a steady absorption of carbon monoxide occurred with some evolution of heat. More gas was pumped in when required. When sufficient had been absorbed the mixture was cooled to 0° and the bulk of the remaining carbon monoxide was pumped back into the storage bulb and a correction applied for the few millimetres' pressure left in the manifold. Finally the reaction mixture was evacuated until the pressure in the system did not exceed that due to the solvent. Samples of the original and the residual carbon monoxide were taken for isotope analysis.

Dry oxygen-free nitrogen was admitted to the manifold and then to the reaction flask, and the apparatus *GH* (Fig. 3) was connected to *D* in place of the stopper in an ascending current of nitrogen. The funnel *G* contained a 100% excess (based on the hydride taken) of tetrahydrofurfuryl alcohol. The apparatus was quickly evacuated and after cooling of trap *E* in liquid nitrogen the alcohol was added to the reaction product with stirring. The mixture of permanent

FIG. 3.



gases which was evolved was transferred by the Töpler pump into the storage bulb until the pressure in the apparatus fell to *ca.* 10 mm. Hg, the vapour pressure of methane at liquid-nitrogen temperature. At this stage the liquid nitrogen around the trap *E* was replaced by solid carbon dioxide, cold water was passed through the finger condenser *F*, and the reaction mixture was stirred at about 60°. Pumping was continued until the pressure in the manifold had fallen to 0·1 mm. Samples of the gaseous product of the reaction were taken for chemical and isotope analysis.

The flask and attachments were then isolated from the manifold and dry nitrogen was admitted at *I*. *E* was cooled in liquid nitrogen, the flask heated to 100° with stirring, and the methanol together with some solvent and tetrahydrofurfuryl alcohol were distilled in a current of nitrogen under conditions of partial reflux into trap *E*. In a typical experiment about 5 g. of distillate were collected containing some 6—10 mmoles of methanol. The methanol was concentrated by distillation *in vacuo* at room temperature as described by Cox, Turner, and Warne [8] but it was not possible to effect a quantitative separation; the yield was therefore determined indirectly. It was first established (Run 1), by preparation of the pure 3 : 5-dinitrobenzoate, that the specific activity of methanol produced in the reaction is identical, within experimental error, with that of the carbon monoxide reduced. The yield of methanol in another experiment (Run 2) was then determined by isotope dilution analysis. A quantity of pure methanol was

added to the first distillate, and a sample of pure methyl 3 : 5-dinitrobenzoate isolated as before; from the specific activities of the diluted methanol and the original carbon monoxide, and the weight of methanol used for dilution, the weight of methanol in the first distillate could be calculated. It was further established by the dilution method that the removal of methanol from the reaction mixture during the first distillation was essentially complete.

(ii) *Experiments with isotopically labelled compounds.* (*a*) Run 1. A solution containing lithium aluminium hydride (11·63 mmoles) was allowed to absorb [^{14}C]carbon monoxide (15·95 mmoles; specific activity $1{\cdot}39 \pm 0{\cdot}01 \times 10^{-7}$, specific activity of residual carbon monoxide $1{\cdot}38 \pm 0{\cdot}01 \times 10^{-7}$) at *ca.* 60° during 1¾ hr. Towards the end of the reaction stirring became difficult owing to the deposition of a large amount of the white reaction complex. The mixture was decomposed by the addition of tetrahydrofurfuryl [^{2}H]alcohol (9·0 ml., *ca.* 100% excess; 76 atoms % deuterium in the hydroxyl group). A total of 11·19 mmoles of gaseous products were formed (see Table 3) of which 99% consisted of hydrogen and saturated hydrocarbons

TABLE 3. *Analyses in Bone and Wheeler apparatus of gaseous products after decomposition* (%).

Gas	CO_2	C_nH_m (unsat.)	O_2	CO	H_2	C_nH_{2n+2}	N_2	n of C_nH_{2n+2}
Run 1	0·1	0·2	0·1	0·3	64·5	34·5	0·3	1·02
Run 2	0·1	0·1	0·0	0·2	75·1	23·4	1·1	1·02

C_nH_{2n+2}. The saturated hydrocarbons ($n = 1{\cdot}02$) must contain at least 98% by volume of methane; the major gaseous products were therefore hydrogen (7·22 mmoles) and methane (3·78—3·86 mmoles). A sample of the mixture of gases was burned to carbon dioxide (specific activity $1{\cdot}29 \pm 0{\cdot}01 \times 10^{-7}$). Mass-spectrometric assay of the mixed gases showed the methane to contain CH_4 (57%) and $CH_3{}^2H$ (43%). The methanol was distilled from the reaction mixture and partially purified by distillation and a sample was converted into the pure 3 : 5-dinitrobenzoate which, on combustion, gave carbon dioxide of specific activity $1{\cdot}71 \pm 0{\cdot}01 \times 10^{-8}$ (corresponding to methanol of specific activity $1{\cdot}37 \pm 0{\cdot}01 \times 10^{-7}$). Mass-spectrometric assay showed the methanol to contain $CH_2{}^2H{\cdot}O^2H$ (25%), $CH_3{\cdot}O^2H$ plus $CH_2{}^2H{\cdot}OH$ (46%), and $CH_3{\cdot}OH$ (29%).

(*b*) Run 2. Lithium aluminium hydride solution (containing 12·83 mmoles of hydride) absorbed at *ca.* 60° [^{14}C]carbon monoxide (12·60 mmoles; specific activity $1{\cdot}40 \pm 0{\cdot}01 \times 10^{-7}$) generated from sodium formate (specific activity $1{\cdot}39 \pm 0{\cdot}01 \times 10^{-7}$); the carbon monoxide remaining at the end of the reaction had specific activity $1{\cdot}38 \pm 0{\cdot}01 \times 10^{-7}$. On adding tetrahydrofurfuryl alcohol (10 ml.) a total of 24·96 mmoles of gaseous products was evolved which (Table 3) contained 18·75 mmoles of hydrogen and 5·84 mmoles of saturated hydrocarbon C_nH_{2n+2}, containing at least 5·72 mmoles of methane, and on combustion gave carbon dioxide of specific activity $1{\cdot}32 \pm 0{\cdot}01 \times 10^{-7}$.

The methanol was distilled from the alcoholysis product, and a total of 4·90 g. of crude product (P_1) was collected. The residue (R_1) from the distillation (total activity *ca.* 8×10^{-9} = *ca.* 0·45% of original total activity in the [^{14}C]carbon monoxide reacting) was mixed with pure methanol (1·00 ml., 24·8 mmoles) and separated by distillation into a residue (R_2) and a methanol fraction (P_2) which was converted into pure methyl 3 : 5-dinitrobenzoate. On combustion this gave carbon dioxide of specific activity $< 5 \times 10^{-12}$; the methanol thus had specific activity $< 4 \times 10^{-12}$ or a total activity of $< 1 \times 10^{-9}$. This is the activity derived from <0·1% of the methanol produced in the reaction. The crude distillate (P_1), which therefore contained at least 99·9% of the methanol produced in the reaction, was mixed with pure methanol (0·740 g.; 23·15 mmoles) and after two distillations gave two residues (R_3 and R_4) and a methanol concentrate (*ca.* 0·7 g.; P_3) which was converted into pure methyl 3 : 5-dinitrobenzoate. On combustion carbon dioxide was obtained with specific activity $3{\cdot}83 \pm 0{\cdot}01 \times 10^{-9}$, corresponding to methanol of specific activity $3{\cdot}06 \pm 0{\cdot}01 \times 10^{-8}$. Assuming the methanol produced in the reaction to have specific activity $1{\cdot}39 \pm 0{\cdot}01 \times 10^{-7}$, the yield was therefore 6·57 mmoles. The residues R_3 and R_4 contained a total activity of *ca.* 3×10^{-7}. This is the activity of *ca.* 10 mmoles of the diluted methanol. The total methanol *after* dilution was 29·7 mmoles, and the amount recovered as a concentrate about 22 mmoles. It is therefore probable that the activity in these residues was largely due to incompletely removed methanol.

A sample of methanol prepared by reduction of carbon monoxide gave a negative reaction for formaldehyde by the chromotropic acid test. Glycol was sought by a dilution method in the less volatile fractions (R_3 and R_4) obtained in the working up of the crude methanol distillate (P_1) in Run 2. By assuming that specific activity of the glycol carbon would be the same as

the original carbon monoxide it was shown that less than 0·03% of the monoxide was converted into glycol. Similarly it was shown that formate present in R_2 was 0·004% of the [^{14}C]carbon monoxide absorbed. This may well have arisen from traces of [^{14}C]carbon dioxide present in the original carbon monoxide.

We thank Dr. J. Idris Jones for his interest, Mr. B. N. Audric and Miss E. Wagner for the carbon-14 analyses, Mr. L. J. Edgcombe of the Fuel Research Station, Department of Scientific and Industrial Research, for the gas analyses, and Mr. W. S. MacDonald for experimental assistance. One of us (A. J. N.) thanks the Department of Scientific and Industrial Research for a vacation studentship. This paper is published by permission of the Director of the Chemical Research Laboratory.

CHEMICAL RESEARCH LABORATORY,
DEPARTMENT OF SCIENTIFIC AND INDUSTRIAL RESEARCH,
TEDDINGTON, MIDDLESEX. [*Received, July 9th*, 1956.]

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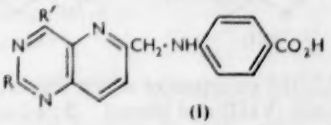
853. *Polyazanaphthalenes. Part IV.*[1] *Further Derivatives of* 1 : 3 : 5- *and* 1 : 3 : 8-*Triazanaphthalene.*

By V. OAKES and H. N. RYDON.

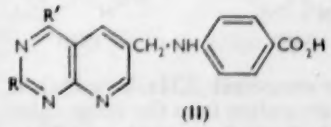
Several 2- and 4-substituted derivatives of 6-methyl-1 : 3 : 5-triazanaphthalene have been synthesised; the 4-hydroxy- and 2 : 4-dihydroxy-compounds have been converted into the corresponding pteroic acid analogues by side-chain bromination, followed by condensation with *p*-aminobenzoic acid. 2 : 4-Dihydroxy- and 2 : 4-dichloro-6-methyl-1 : 3 : 8-triazanaphthalene have also been synthesised but attempts to convert them similarly into pteroic acid analogues were not successful.

A theoretical explanation is given for the preferential reactivity of the 4-chlorine atom in the 2 : 4-dichloro-derivatives of quinazoline, 1 : 3 : 5-triazanaphthalene, and 1 : 3 : 8-triazanaphthalene.

THE work described in this paper had as its objective the synthesis of pteroic acid analogues of the general types (I) and (II), containing the 1 : 3 : 5- and the 1 : 3 : 8-triazanaphthalene ring system, respectively, in place of the pteridine (1 : 3 : 5 : 8-tetrazanaphthalene) ring system present in pteroic acid itself. The general chemistry of these two ring systems, and convenient synthetic routes to them, have been described in Part III of this series.[1] The route envisaged for the synthesis of the required pteroic acid analogues involved synthesis of appropriately 2- and 4-substituted 6-methyl compounds, followed by side-chain bromination and condensation with *p*-aminobenzoic acid.[2]



(I)

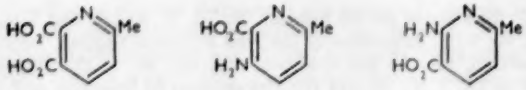


(II)

The most convenient starting material for the synthesis of derivatives of 6-methyl-1 : 3 : 5-triazanaphthalene is 8-hydroxy-2-methylquinoline.[3] Nitric acid oxidation by the procedure used by Sucharda [4] for the oxidation of 8-hydroxyquinoline was unsatisfactory but in carbon tetrachloride gave satisfactory yields of 6-methylquinolinic acid (III). Some difficulty was encountered in the conversion of this acid into its imide; fusion of the ammonium salt resulted in extensive decomposition, while reaction of the anhydride with acetamide [4] gave very variable yields. The best yields were finally obtained by heating the diamide just below its melting point; [5] actual fusion of the diamide resulted in a

[1] Part III, Oakes, Pascoe, and Rydon, *J.*, 1956, 1045.
[2] Cf. Boothe *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 27.
[3] Doebner and Müller, *Ber.*, 1884, **17**, 1706.
[4] Sucharda, *Ber.*, 1925, **58**, 1728.
[5] Cf. Engler, *Ber.*, 1894, **27**, 1788.

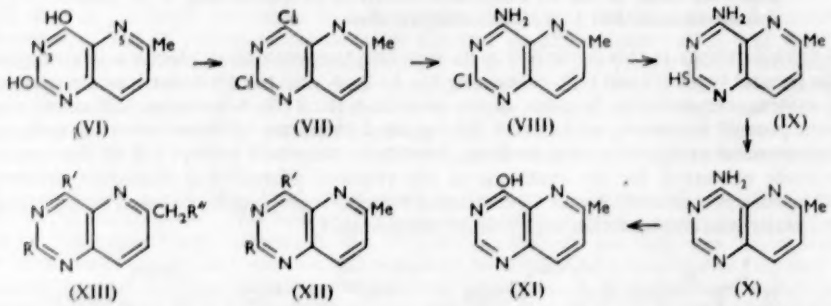
considerably diminished yield. Treatment of 6-methylquinolinimide with sodium hypobromite might yield either the desired 3-amino-6-methylpicolinic acid (IV) or the isomeric 2-amino-6-methylnicotinic acid (V), the former being the more probable product by analogy



(III) (IV) (V)

with the course of the similar reaction with quinolinimide.[1] That the reaction took the expected, and desired, course was shown by decarboxylation, which gave a product, m. p. 95°, which was clearly 5-amino-2-picoline (lit.,[6] m. p. 96°) and not the 6-amino-compound (lit.,[7] m. p. 41°).

2 : 4-Dihydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (VI) was readily prepared by fusion of 3-amino-6-methylpicolinic acid (IV) with urea and converted into the 2 : 4-dichloro-compound (VII) in satisfactory yield by treatment with phosphorus oxychloride in the presence of triethylamine.[1,8] As with the unmethylated compound,[1] the two chlorine atoms in (VII) differed markedly in reactivity towards nucleophilic reagents, that in position 4 being the more reactive. Thus, treatment with ammonia in cold dioxan yielded the 4-amino-2-chloro-compound (VIII) which, on treatment with thiourea, afforded the 4-amino-2-mercapto-compound (IX); Raney nickel desulphurisation of the last-named compound gave the 4-amino-compound (X) which was converted by boiling dilute acid into 4-hydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (XI), identical with material prepared by fusing 3-amino-6-methylpicolinic acid with formamide, this identity confirming the structures assigned to (VIII), (IX), and (X). Treatment of the dichloro-compound (VII) with ammonia in boiling phenol [1,9] yielded, not the expected diamine, but the 4-amino-2-



(VI) (VII) (VIII) (IX) (X) (XI) (XII) (XIII)

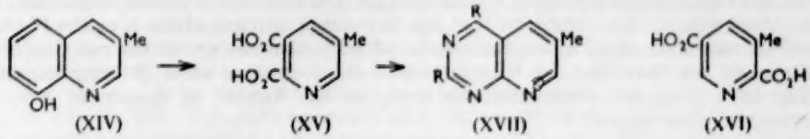
phenoxy-compound (XII; R = PhO, R′ = NH_2), the structure of which was established by its preparation from the amino-chloro-compound (VIII) and phenol. 2 : 4-Diamino-6-methyl-1 : 3 : 5-triazanaphthalene (XII; R = R′ = NH_2) was finally obtained in excellent yield by heating the dichloro-compound (VII) or the amino-chloro-compound (VIII) at 170° with ethanolic ammonia.[10]

Side-chain bromination of the 4-hydroxy- (XI) and the 2 : 4-dihydroxy-compound (VI) gave smoothly the corresponding 6-bromomethyl compounds (XIII; R″ = Br); these resisted attempted purification but the presence of the side-chain bromine in the 2 : 4-dihydroxy-compound (XIII; R = R′ = OH, R″ = Br) was confirmed by its conversion into the 2 : 4-dihydroxy-6-hydroxymethyl compound (XIII; R = R′ = R″ = OH) by

[6] Graf, *J. prakt. Chem.*, 1932, **133**, 19.
[7] Meyer, *Rec. Trav. chim.*, 1925, **44**, 323.
[8] Cf. Robins and Christensen, *J. Amer. Chem. Soc.*, 1952, **74**, 3624.
[9] Cf. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.
[10] Cf. Robins and Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2256.

boiling water. Condensation of the crude 6-bromomethyl compounds with *p*-aminobenzoic acid [9] afforded two pteroic acid analogues containing the 1 : 3 : 5-triazanaphthalene skeleton, *viz.*, (I; R = H, R′ = OH) and (I; R = R′ = OH).

These two pteroic acid analogues were kindly tested for anti-folic acid activity by Dr. O. R. Bird of Messrs. Parke, Davis & Co. of Detroit, to whom we express our best thanks; both were inactive (inhibition index for *Streptococcus faecalis* greater than 75,000).



(XIV) (XV) (XVII) (XVI)

8-Hydroxy-3-methylquinoline (XIV), the most convenient starting material for the synthesis of derivatives of 6-methyl-1 : 3 : 8-triazanaphthalene, was prepared in very poor yield by the Skraup reaction between *o*-aminophenol and α-methylacraldehyde. Oxidation with fuming nitric acid [4] gave a good yield of 5-methylquinolinic acid (XV), m. p. 181°. Durkopf and Göttsch [11] assigned (XV) as one of two possible structures to the methylpyridinedicarboxylic acid, m. p. 223°, obtained [12] by oxidation of 2-ethyl-3 : 5-dimethylpyridine; the non-identity of the melting points establishes (XVI) (3-methylpyridine-2 : 5-dicarboxylic acid) as the structure of this oxidation product. Treatment of the diamide of (XV) with sodium hypobromite [1,13] afforded 2 : 4-dihydroxy-6-methyl-1 : 3 : 8-triazanaphthalene (XVII; R = R′ = OH) which was readily converted into the dichloro-compound (XVII; R = R′ = Cl); as with the unmethylated compound [1] hydrogenation failed to remove the nuclear chlorine atoms, giving, in this case, a dihydro-compound. Not unexpectedly, neither the dihydroxy- nor the dichloro-compound (XVII) could be halogenated in the side-chain, although several methods were tried; further work in this series was therefore abandoned.

In Part III [1] the greater reactivity towards nucleophilic reagents of the 4-chlorine, as compared with the 2-chlorine atom, in 2 : 4-dichloro-1 : 3 : 5- and -1 : 3 : 8-triazanaphthalenes was accounted for by extension of the explanation advanced by Curd, Landquist, and Rose [14] for the similar preferential reactivity of the 4-chlorine atom in 2 : 4-dichloroquinazoline. A more satisfying explanation results by applying the simplified Longuet-Higgins quantum-mechanical treatment [15] which has been extended to several other halogeno-polyazanaphthalenes by Chapman.[16] The results of these calculations are given in the following Table, in which δ^{N}, δ^{Cl}, and δ^{Me} represent the perturbations in charge-

2 : 4-Dichloro-compound of	Nucleophilic substitution of	$\Delta U - \Delta U_0$	$\Delta U_{4Cl} - \Delta U_{2Cl}$
Quinazoline	2-Cl	$0{\cdot}63\delta^{N} + 0{\cdot}08\delta^{Cl}$	$0{\cdot}10\delta^{N} + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}73\delta^{N} + 0{\cdot}24\delta^{Cl}$	
1 : 3 : 5-Triazanaphthalene	2-Cl	$0{\cdot}71\delta^{N} + 0{\cdot}08\delta^{Cl}$	$0{\cdot}08\delta^{N} + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}79\delta^{N} + 0{\cdot}24\delta^{Cl}$	
6-Methyl-1 : 3 : 5-triazanaphthalene	2-Cl	$0{\cdot}71\delta^{N} + 0{\cdot}08\delta^{Cl} - 0{\cdot}13\delta^{Me}$	$0{\cdot}08\delta^{N} + 0{\cdot}16\delta^{Cl} + 0{\cdot}04\delta^{Me} + \delta'$
	4-Cl	$0{\cdot}79\delta^{N} + 0{\cdot}24\delta^{Cl} - 0{\cdot}09\delta^{Me}$	
1 : 3 : 8-Triazanaphthalene	2-Cl	$0{\cdot}75\delta^{N} + 0{\cdot}08\delta^{Cl}$	$0{\cdot}07\delta^{N} + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}82\delta^{N} + 0{\cdot}24\delta^{Cl}$	

density distribution in the transition state at the point of substitution for a ring-nitrogen atom, a chlorine atom, and a methyl group, respectively, that for the last-named being opposite in sign from those for the other two. The values of $\Delta U - \Delta U_0$ (third column) are measures of the calculated differences in the activation energies, at 0° K, of the reactions

[11] Durkopf and Göttsch, *Ber.*, 1890, **23**, 1111.
[12] *Idem, ibid.*, p. 688; Durkopf and Schlaugk, *Ber.*, 1888, **21**, 834.
[13] McLean and Spring, *J.*, 1949, 2582.
[14] Curd, Landquist, and Rose, *J.*, 1947, 775.
[15] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 283.
[16] Chapman, *Chem. Soc. Spec. Publ.*, No. 3, 1955, p. 155; Chapman and Russell-Hill, *J.*, 1956, 1563.

of the chlorine atoms indicated with nucleophilic reagents and the corresponding reactions of the reference compounds, *viz.*, 1- and 2-chloronaphthalene for the 4- and 2-chloroheterocycles, respectively. The differences, $\Delta U_{4Cl} - \Delta U_{2Cl}$ (last colmun), are then measures of the calculated differences in activation energy between the reactions of the 4- and the 2-chlorine atoms in the four dichloropolyazanaphthalenes with a given nucleophilic reagent, the additional term, δ', representing the (relatively small) differences in activation energy between the corresponding reactions of the two reference chloronaphthalenes; the major effect will, without doubt, be that due to the ring nitrogen atoms (*i.e.*, the δ^N term). It will be seen that, in all cases, the calculated activation energy for the reaction of the 4-chlorine is less than that for the reaction of the 2-chlorine atom (δ being negative), leading to a predicted preferential reactivity of the former, in agreement with the experimental observations.

Experimental

1 : 3 : 5-*Triazanaphthalene Derivatives.*

6-*Methylquinolinic Acid* (III).—8-Hydroxy-2-methylquinoline [3] (20 g.), in carbon tetrachloride (50 ml.), was added dropwise, with ice-cooling and vigorous mechanical stirring, to fuming nitric acid (100 ml.). After being stirred for a further 30 min., the mixture was concentrated on the steam-bath to 50 ml. Water (300 ml.) was then added and the filtered solution evaporated to dryness; treatment of the resulting gum with a little ethanol gave the *acid* (10 g., 44%) which crystallised from ethanol in needles, m. p. 164° (Found : C, 52·9; H, 4·0; N, 7·6. $C_8H_7O_4N$ requires C, 53·0; H, 3·9; N, 7·7%).

6-*Methylquinolinimide.*—(*a*) 6-Methylquinolinic acid (15 g.) was refluxed with acetic anhydride (50 ml.) for 6 hr.; the resulting clear solution was evaporated to dryness under reduced pressure and the residue heated at 125—130° for 8 hr. with acetamide (15 g.). The mixture was cooled, poured into water, and filtered and the filtrate extracted continuously with ether for 4 hr. The product obtained by evaporation of the extract was added to the solid obtained by filtration, and the mixture recrystallised from ethyl acetate, affording the *imide* (6 g., 46%), m. p. 244° (Found : C, 58·8; H, 3·6. $C_8H_6O_2N_2$ requires C, 59·2; H, 3·7%); the yield was very variable.

(*b*) 6-Methylquinolinic acid (4 g.) was refluxed on the steam-bath for 4 hr. with ethanol (10 g.) and sulphuric acid (10 g.). The cooled product was poured on ice, basified with aqueous ammonia, and extracted with ether. The crude ester obtained by evaporating the extract was suspended in aqueous ammonia solution (*d* 0·880; 40 ml.) and ammonia passed through the suspension for 5 hr. 6-*Methylquinolindiamide* separated (1·8 g., 46%) and crystallised from water in needles, m. p. 210° (Found : C, 53·4; H, 4·8. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·0%).

This amide (20 g.) was heated at 210—215° until evolution of ammonia ceased. The product was cooled, crushed, and recrystallised from ethyl acetate, affording the imide (18 g., 99·5%), prisms, m. p. 244°.

3-*Amino-6-methylpicolinic Acid* (IV).—Aqueous sodium hypobromite (from bromine, 5·6 ml., and ice-cold 2N-sodium hydroxide, 120 ml.) was added to a solution of 6-methylquinolinimide (16 g.) in ice-cold 2N-sodium hydroxide (300 ml.), and the mixture kept at room temperature for an hour and then at 80° for a further hour. After cooling, the pH was brought to 5 with 50% sulphuric acid, and the mixture kept at 2° for 24 hr. The small amount of precipitate was filtered off and the filtrate treated with copper acetate (6 g.), in hot water (150 ml.) containing acetic acid (6 ml.). The precipitated copper salt was collected, washed with water, and resuspended in water (150 ml.); the suspension was then saturated with hydrogen sulphide. Copper sulphide was removed and the filtrate decolorised with charcoal and evaporated to dryness. The resulting *acid* (7·5 g., 50%) crystallised from ethanol in pale yellow prisms, m. p. 205° (Found : C, 55·4; H, 5·2. $C_7H_8O_2N_2$ requires C, 55·3; H, 5·3%).

This acid (200 mg.) was heated in a long tube at 230° for 10 min. and then at 270° for 20 min. The distillate was crystallised from benzene–light petroleum (b. p. 60—80°), yielding 5-amino-2-picoline as plates, m. p. 95° (lit.,[4] m. p. 96°).

2 : 4-*Dihydroxy-6-methyl*-1 : 3 : 5-*triazanaphthalene* (VI).—3-Amino-6-methylpicolinic acid (5 g.) was intimately mixed with urea (3 g.), heated slowly to 190—200°, and kept at this temperature for an hour. The cooled product was dissolved in 2N-sodium hydroxide (50 ml.) and decolorised with charcoal. Saturation with carbon dioxide precipitated the *dihydroxy-compound* (2·2 g., 38%) which crystallised from water in needles, m. p. >370° (Found : C, 54·7; H, 3·6. $C_8H_7O_2N_3$ requires C, 54·2; H, 3·95%).

2 : 4-*Dichloro*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (VII).—The dihydroxy-compound (VI) (500 mg.) was heated under reflux for 6 hr. with phosphorus oxychloride (15 ml.) and triethylamine (1 ml.). The product was evaporated to dryness under reduced pressure and the residue heated at 100°/12 mm. for an hour. The cooled residue was treated with ice-water (15 ml.), and the insoluble portion collected, dried at the pump, and sublimed at 140° (bath)/0·1 mm. The resulting *dichloro-compound* (300 mg., 50%), recrystallised from light petroleum (b. p. 80—100°), had m. p. 138° (Found : C, 45·1; H, 2·5. $C_8H_5N_3Cl_2$ requires C, 44·8; H, 2·3%).

4-*Amino*-2-*chloro*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (VIII).—Ammonia was passed for 15 min. through a solution of the dichloro-compound (VII) (190 mg.) in anhydrous dioxan (20 ml.). The product was evaporated to dryness under reduced pressure; treatment of the residue with water (15 ml.), filtration, and washing with water afforded the *amino-chloro-compound* (150 mg., 87%) which crystallised from benzene in needles, m. p. 261° (Found : C, 49·7; H, 3·7; N, 28·8. $C_8H_7N_4Cl$ requires C, 49·2; H, 3·6; N, 28·6%).

4-*Amino*-2-*mercapto*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (IX).—The amino-chloro-compound (VIII) (150 mg.) was refluxed for 5 hr. with thiourea (150 mg.) in ethanol (25 ml.). The *amino-mercapto-compound* (90 mg., 61%) was slowly deposited from the resulting solution as yellow prisms, m. p. >400° (Found : N, 29·0. $C_8H_8N_4S$ requires N, 29·1%).

4-*Amino*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (X).—The amino-mercapto-compound (IX) (90 mg.) and Raney nickel (1 g.), suspended in ethanol (40 ml.) and aqueous ammonia (*d* 0·880; 10 ml.), were heated under reflux for 2 hr. The cooled product was filtered and the solid washed with hot ethanol (3 × 10 ml.); evaporation of the filtrate and washings under reduced pressure, followed by recrystallisation from benzene–light petroleum (b. p. 60—80°), afforded the *amine* (50 mg., 67%), m. p. 184° (Found : C, 60·3; H, 4·8; N, 34·9. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%). This amine was heated for an hour with 5N-hydrochloric acid; concentration and addition of sodium carbonate afforded the 4-hydroxy-compound (IX) (see below), m. p. and mixed m. p. 296—297°.

4-*Hydroxy*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (XI).—3-Amino-6-methylpicolinic acid (1·5 g.) and formamide (1 g.) were heated together at 125° for 2·5 hr. and then at 180° for 2·5 hr. On cooling, the *hydroxy-compound* (700 mg., 44%) was deposited as needles which were washed with ethanol and recrystallised from water, yielding plates, m. p. 299° (Found : C, 59·7; H, 4·5; N, 26·2. $C_8H_7ON_3$ requires C, 59·6; H, 4·4; N, 26·1%).

4-*Amino*-6-*methyl*-2-*phenoxy*-1 : 3 : 5-*triazanaphthalene* (XII; R = PhO, R′ = NH_2).—(*a*) Ammonia was passed for 2 hr. through a solution of the dichloro-compound (VII) (250 mg.) in boiling phenol (10 g.). The cooled product was treated with an excess of 10% sodium hydroxide solution, and the precipitated amino-phenoxy-compound (90 mg.) collected by filtration and recrystallised from methanol in needles, m. p. and mixed m. p. 231°.

(*b*) The amino-chloro-compound (VIII) (50 mg.) was heated for 3 hr. in boiling phenol (2·5 g.). The cooled product was treated with excess of 10% sodium hydroxide solution, and the insoluble *amino-phenoxy-compound* (50 mg., 77%) collected and recrystallised from benzene–light petroleum (b. p. 60—80°), forming prisms, m. p. 231° (Found : C, 67·5, 67·5; H, 4·7, 4·6; N, 22·8. $C_{14}H_{13}ON_4$ requires C, 66·8; H, 4·7; N, 22·2%).

2 : 4-*Diamino*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (XII; R = R′ = NH_2).—The dichloro-compound (VII) (765 mg.) or the amino-chloro-compound (VIII) (700 mg.) was heated in a sealed tube at 170° for 16 hr. with saturated ethanolic ammonia (15 ml.). The cooled product was filtered and the solid washed with water, dried, and recrystallised from benzene–ethanol, affording the *diamine* (600 mg., 95%) as needles, m. p. 241° (Found : C, 55·5; H, 4·8; N, 40·2. $C_8H_9N_5$ requires C, 54·9; H, 5·1; N, 40·0%). The *monohydrobromide* had m. p. 285° (Found : C, 38·5; H, 4·0; N, 27·3. $C_8H_{10}N_5Br$ requires C, 37·5; H, 3·9; N, 27·3%).

2 : 4-*Dihydroxy*-6-*hydroxymethyl*-1 : 3 : 5-*triazanaphthalene* (XIII; R = R′ = R″ = OH).—The dihydroxy-compound (VI) (177 mg.), bromine (0·06 ml.), and sodium acetate (100 mg.) were heated on the steam-bath, in acetic acid (30 ml.), for 2 hr. The acetic acid was then removed under reduced pressure and the residue ground and washed with water until free from inorganic matter. Recrystallisation from boiling water afforded the *hydroxymethyl compound* (110 mg., 57%) as needles, m. p. 330° (Found : C, 50·0, 49·9; H, 4·0, 3·9. $C_8H_7O_3N_3$ requires C, 49·7; H, 3·6%).

Pteroic Acid Analogues.—(*a*) 4-Hydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (500 mg.), sodium acetate (250 mg.), and bromine (0·186 ml.) were heated in acetic acid (50 ml.) on the steam-bath for an hour, by which time all the bromine had reacted. *p*-Aminobenzoic acid (425 mg.) was then added and heating continued for a further 2 hr. Next day, a little *p*-aminobenzoic acid hydrobromide was filtered off and the filtrate evaporated to dryness under reduced

pressure. The residue was treated with hot water (25 ml.), and the solid collected and washed thoroughly with hot water. Reprecipitation from alkaline solution with acetic acid afforded p-(*4-hydroxy*-1 : 3 : *5-triaza-6-naphthylmethylamino*)*benzoic acid* (I; R = H, R′ = OH) (50 mg., 6%) as a yellow powder, m. p. 265° (Found: C, 52·5, 52·9; H, 4·4, 4·5; N, 16·7, 16·5. $C_{15}H_{13}O_3N_4,2{\cdot}5H_2O$ requires C, 52·8; H, 5·0; N, 16·4%).

(*b*) 2 : 4-Dihydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (530 mg.), sodium acetate (200 mg.), and bromine (0·18 ml.) were heated on the steam-bath in acetic acid (50 ml.) for 4 hr. Condensation with *p*-aminobenzoic acid (410 mg.), followed by working up in the usual manner, afforded p-(*2 : 4-dihydroxy*-1 : 3 : *5-triaza-6-naphthylmethylamino*)*benzoic acid* (I; R = R′ = OH) (250 mg., 30%), m. p. >380° (Found: C, 52·6, 52·7; H, 4·1, 4·1; N, 16·4. $C_{15}H_{12}O_4N_4,1{\cdot}5H_2O$ requires C, 53·1; H, 4·4; N, 16·5%).

1 : 3 : 8-*Triazanaphthalene Derivatives.*

8-*Hydroxy*-3-*methylquinoline* (XIV).—*o*-Aminophenol (50 g.), *o*-nitrophenol (25 g.), α-methylacraldehyde (40 ml.), and concentrated hydrochloric acid (100 ml.) were heated together under reflux for 90 min. The product was steam-distilled to remove excess of *o*-nitrophenol, and the residue then basified with sodium carbonate. Further steam-distillation afforded the *base* (6·5 g., 9%) which crystallised from ethanol in needles, m. p. 110° (Found: C, 75·3; H, 5·6; N, 9·2. $C_{10}H_9ON$ requires C, 75·5; H, 5·7; N, 8·8%).

5-Methylquinolinic Acid (XV).—8-Hydroxy-3-methylquinoline (6 g.) was treated dropwise with fuming nitric acid (20 ml.) during 2 hr. After a further hour, the mixture was heated on the steam-bath until evolution of nitrous fumes was complete. The mixture was then cooled and treated with more fuming nitric acid (30 ml.), added in a steady stream. After 3 hr. at room temperature the mixture was evaporated to dryness on the steam-bath. Treatment of the residue with water afforded the *acid* (4 g., 60%), which crystallised from ethanol in plates, m. p. 181° (Found: C, 53·1; H, 3·9. $C_8H_7O_4N$ requires C, 53·0; H, 3·9%).

5-Methylquinolinamide.—5-Methylquinolinic acid (3 g.) was refluxed on the steam-bath for 4 hr. with ethanol (9 g.) and sulphuric acid (5 g.). The cooled product was poured on ice and basified with aqueous ammonia. The crude ester, isolated by extraction with ether, was suspended in ammonia solution (*d* 0·880; 30 ml.), and gaseous ammonia was passed into the mixture for 5 hr. The *amide* (0·8 g., 27%) separated and crystallised from water in needles, m. p. 181° (Found: C, 53·5; H, 4·6. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·0%).

2 : 4-*Dihydroxy*-6-*methyl*-1 : 3 : 8-*triazanaphthalene* (XVII; R = OH).—5-Methylquinolinamide (700 mg.) and sodium hypobromite solution (20 ml.; from bromine, 0·6 g., and 2N-sodium hydroxide, 20 ml.) were mixed and kept at room temperature for 1 hr. and then at 80° for 1 hr. After cooling, saturation with carbon dioxide precipitated the *dihydroxy-compound* (400 mg., 58%) which crystallised from water in needles, m. p. 345° (Found: C, 53·9; H, 3·7. $C_8H_7O_2N_3$ requires C, 54·2; H, 3·95%).

2 : 4-*Dichloro*-6-*methyl*-1 : 3 : 8-*triazanaphthalene* (XVII; R = Cl).—The dihydroxy-compound (250 mg.) was refluxed for 5 hr. with phosphorus oxychloride (20 ml.). The product was evaporated under reduced pressure and the residue treated with sodium hydrogen carbonate (3 g.) in water (10 ml.) and filtered. The filtrate was extracted with ethyl acetate, and the extract added to the solid from the filtration. Sublimation at 160° (bath)/0·1 mm. afforded the *dichloro-compound* (70 mg., 23%), m. p. 141° (Found: C, 44·1; H, 2·2. $C_8H_5N_3Cl_2$ requires C, 44·8; H, 2·3%).

This compound (100 mg.), in ethanol (50 ml.), was shaken in hydrogen over Adams catalyst (50 mg.); 24 ml. of hydrogen were absorbed. Filtration and evaporation afforded a 2 : 4-*dichloro*-x : y-*dihydro*-6-*methyl*-1 : 3 : 8-*triazanaphthalene* which crystallised from methanol in prisms, m. p. 234° (Found: C, 44·3; H, 3·15. $C_8H_7N_3Cl_2$ requires C, 44·4; H, 3·25%).

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854. *Structural Chemistry of the Alkoxides. Part VIII.* Isomeric Butoxides and Pentyloxides of Niobium.*

By D. C. Bradley, B. N. Chakravarti, and W. Wardlaw.

The isomeric butoxides and pentyloxides (excepting the *tert.*-alkoxides) of niobium have been prepared and their molecular weights in boiling benzene and their volatilities have been determined. The physicochemical properties of the niobium alkoxides are compared with those of the corresponding tantalum derivatives. In contrast to tantalum, which forms stable penta-*tert.*-alkoxides, niobium gives oxy-derivatives with tertiary alkoxides and no penta-*tert.*-alkoxides of niobium could be isolated. This difference is discussed from the theoretical standpoint and is related to the lower thermal stability of *n*-alkoxides of niobium.

The preparation and properties of *n*-alkoxides of niobium [1] and of tantalum [2] and the isomeric butoxides and pentyloxides of tantalum [3] have recently been described. We now describe the isomeric butoxides and pentyloxides of niobium and make an extensive comparison between the alkoxides of niobium and of tantalum. A feature of the *n*-alkoxides was the variation in relative volatility of niobium and tantalum compounds with the chain length of the alkyl group and it was of interest to gain further information for branched-chain derivatives. It was also noteworthy that niobium *n*-alkoxides seemed less stable thermally than the tantalum derivatives, presumably owing to electronic factors, and it was expected that this contrast in behaviour would be affected by the enhanced inductive effects of branched-chain alkyl groups.

The new alkoxides of niobium were prepared either from the pentachloride by the ammonia method [1] or by alcohol interchange on the pentaethoxide.[1] The molecular weights were determined ebullioscopically in benzene, and boiling points were measured at pressures near 0·1 mm. The low thermal stability of the alkoxides precluded measurements at higher pressures.

Isomeric Butoxides.—The molecular complexities and boiling points of the isomeric butoxides of niobium and tantalum are presented in Table 1, in which a striking feature is

Table 1.

R in $M(OR)_5$	B. p./0·1 mm. Nb	B. p./0·1 mm. Ta	Mol. complexity Nb	Mol. complexity Ta
$Me{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2$	195°	215°	2·01	2·02
$Me_2CH{\cdot}CH_2$	160 *	185 †	1·83	2·04
MeEtCH	112·5	137·5	1·14	1·06
Me_3C	—	96 ‡	—	1·00

* M. p. 150°. † M. p. 157°. ‡ Temp. of sublimation.

the absence of niobium *tert.*-butoxide. In spite of several variations in preparative procedure we have not been able to isolate a penta-*tert.*-butoxide, the products always being oxide *tert.*-butoxides such as $Nb_2O(OBu^t)_8$ and $NbO(OBu^t)_3$. For the present we assume that the penta-*tert.*-butoxide, if it exists, is insufficiently stable to survive normal preparative procedure. On the other hand, tantalum forms a relatively stable penta-*tert.*-butoxide which may be distilled unchanged [3] at 5·5 mm., and this behaviour of the *tert.*-butoxides appears to constitute a major chemical difference between niobium and tantalum and will be further discussed under the isomeric pentyloxides. Another feature of Table 1 is that the b. p. of the niobium butoxide is invariably lower than that of the corresponding tantalum derivative. These are further examples of volatile compounds which may be suitable for the separation of niobium from tantalum by distillation. A similarity between niobium and tantalum is reflected in the parallel increase in volatility with increased

* Part VII, *J.*, 1956, 3469.

[1] Bradley, Chakravarti, and Wardlaw, *J.*, 1956, 2381.
[2] Bradley, Wardlaw, and Whitley, *J.*, 1955, 726.
[3] *Idem, ibid.*, 1956, 1139.

branching of the butyl group coupled with a corresponding decrease in molecular complexity. In each case the greatest change occurs in passing from *iso*butoxide to *sec.*-butoxide. However, the molecular complexity of niobium *sec.*-butoxide appears anomalously high. A further similarity is in the crystalline nature of the *iso*butoxides which are close in melting point.

Isomeric Pentyloxides.—The data on these oxides are given in Table 2. The pentyl-

TABLE 2.

R in $M(OR)_5$	B. p./0·1 mm. Nb	B. p./0·1 mm. Ta	ΔT	Mol. complexity Nb	Mol. complexity Ta
$Me\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2$	228°	233°	5·0°	2·00	2·01
$Me_2CH\cdot CH_2\cdot CH_2$	199	210	11·0	1·81	1·98
$MeEtCH\cdot CH_2$	183	204	21·0	1·81	1·97
$Me_2C\cdot CH_2$	126 *	130 †	4·0	1·52	1·35
Et_2CH	138	153	15·0	1·16	1·02
$MePr^nCH$	137·5	148	10·5	1·03	0·99
$MePr^iCH$	139	137	−2·0	1·05	1·02
$MeEt_2C$	—	139	—	—	1·00

* M. p. 90°. † M. p. 120°.

oxides of niobium resemble the tantalum derivatives in showing the expected variation of volatility and molecular complexity with branching of the pentyl group. In each case there is a marked change in passing from the derivative of 2-methylbutan-1-ol (*sec.*-butylcarbinol) to the *neo*pentyloxide which suggests that stereochemical factors are primarily responsible for the change. Both *neo*pentyloxides are anomalous in exhibiting greater molecular complexities but lower b. p.s than the secondary pentyloxides and this is probably related to the high m. p.s of the *neo*pentyloxides (cf. ref. 3). A further anomaly is the higher complexity of the niobium derivative of pentan-3-ol (diethylcarbinol) compared with the tantalum compound and this recalls the behaviour of the *sec.*-butoxides (Table 1). The differences in b. p. (ΔT = b. p. of Ta compd. − b. p. of Nb compd.) are also shown in Table 2, and it is noticeable that niobium alkoxides are closer in b. p. to the corresponding tantalum compounds in the pentyloxides than in the butoxides. The most interesting feature of the pentyloxides is the apparent non-existence of niobium penta-*tert.*-amyloxide. Attempts to obtain this compound under the mildest conditions always produced an oxide *tert.*-amyloxide. Moreover, a similar result was obtained with 3-ethylpentan-3-ol (triethylcarbinol) and it appears that penta-*tert.*-alkoxides of niobium are unstable and break down to oxy-compounds in contrast to the stability of the corresponding tantalum derivatives. This calls to mind the behaviour of the complex fluorides, *e.g.*, $K_2[MF_7]$, in which the niobium compound readily passes into the more stable oxyfluoroniobate $K_2[NbOF_5]$, and also the fact that in general niobium has a much stronger tendency than tantalum to form oxy-compounds. In connection with the *n*-alkoxides of niobium and tantalum [1] we have already suggested that the tendency of niobium to form oxy-compounds promotes the release of a carbonium ion from a Nb–O–C system, *viz.*:

$$^-Nb=^+OR \longrightarrow ^-Nb=O + R^+$$

The behaviour of the niobium *tert.*-alkoxides is consistent with this view because of the enhanced tendency of the *tert.*-alkyl group to assume the carbonium structure. Thus it is expected that the stability of a niobium alkoxide will be decreased by alkyl groups having pronounced $+I$ inductive effects. With this idea in mind we attempted to prepare the niobium derivative of 1-phenylethanol which should behave like a secondary alcohol with a strong $+I$ effect. Under mild conditions the penta-(1-phenylethoxide) of niobium was obtained as a material which decomposed when heated. It is clear that a detailed investigation is required to explain fully this interesting behaviour of niobium *tert.*-alkoxides, but our experiments show that electronic factors rather than stereochemical factors are responsible. The possibility of utilising this contrast between niobium and tantalum for separating these elements is now being investigated, but it is also feasible that the niobium oxide *tert.*-alkoxides may act as catalysts for the breakdown of the more stable *tert.*-alkoxides of tantalum and thus prevent easy separation.

Experimental

The general experimental details are the same as those reported previously.[1]

Niobium Pentaisobutoxide.—Niobium pentachloride (7·9 g.), suspended in benzene (200 c.c.), was treated with *iso*butyl alcohol (50 c.c.) and then excess of ammonia. After removal of ammonium chloride by filtration the filtrate was evaporated to dryness and gave a grey chloride-free solid (12·65 g.) which was recrystallised from *iso*butyl alcohol (100 c.c.). After five crystallisations a pure white solid (8·6 g.) was obtained [Found: Nb, 20·2. $Nb(OC_4H_9)_5$ requires Nb, 20·3%].

Niobium Penta-(1-methylpropoxide).—The new *alkoxide* was obtained as a pale yellow liquid (13·8 g.) from the reaction involving the pentachloride (9·9 g.), *sec.*-butyl alcohol (50 c.c.), and excess of ammonia in benzene (200 c.c.). Distillation (98·5°/0·02 mm.) gave a chloride-free liquid (11·9 g.) (Found: Nb, 20·2%).

Niobium Penta-tert.-butoxide.—(*a*) The reaction involving the pentachloride (6·7 g.) suspended in light petroleum (b. p. 40—60°, 200 c.c.) with *tert.*-butyl alcohol (50 c.c.) and excess of ammonia gave a dark, chloride-free solid (7·5 g.) [Found: Nb, 28·1. $NbO(OC_4H_9)_3$ requires Nb, 28·3%].

(*b*) The pentachloride (4·6 g.) was added to pyridine (125 c.c.) and after the addition of *tert.*-butyl alcohol (50 c.c.) the mixture was treated with excess of ammonia. After removal of ammonium chloride by filtration the filtrate was evaporated to dryness. The product was dissolved in benzene (200 c.c.) and treated with *tert.*-butyl alcohol (10 c.c.) and ammonia. A further amount of ammonium chloride was filtered off and the filtrate when taken to dryness gave a black solid (Found: Nb, 25·4; Cl, 2·2%). Pyridine was used in expt. (*b*) to avoid possible side reactions between hydrogen chloride and the tertiary alcohol leading to the formation of water which could have occurred in expt. (*a*).

(*c*) With the utmost precautions to prevent hydrolysis the pentachloride (7·9 g.) in pyridine (100 c.c.) was mixed with ice-cold benzene–*tert.*-butyl alcohol azeotrope and then treated with ammonia twice as in expt. (*b*). The final black solid product (9·75 g.) was not the pentabutoxide (Found: Nb, 22·5; Cl, 2·2%). In another similar experiment a dark chloride-free *product* was obtained [Found: Nb, 23·7. $Nb_2O(Bu)_8$ requires Nb, 23·6%]. Another experiment involving the reaction between the pentachloride and sodium *tert.*-butoxide in benzene also failed to yield the penta-*tert.*-butoxide.

Niobium Pentaisopentyloxide.—*iso*Pentyl alcohol (42 g.) was added dropwise to the pentachloride (6·9 g.) suspended in benzene (200 c.c.), and the solution treated with excess of ammonia. The new *alkoxide*, isolated in the usual manner, was distilled (206°/0·2 mm., some decomp.) and gave a red, chloride-free distillate [Found: Nb, 18·1. $Nb(OC_5H_{11})_5$ requires Nb, 17·6%].

Niobium Penta-(2-methylbutoxide).—The pentachloride (5·9 g.), 2-methylbutan-1-ol (30 g.), and ammonia were allowed to react in benzene (200 c.c.) in the foregoing manner and the new *alkoxide* was isolated as a viscous red liquid and then distilled (169°/0·02 mm.) (Found: Nb, 17·9%).

Niobium Pentaneopentyloxide.—*neo*Pentyl alcohol (12·3 g.) was caused to react with niobium pentaethoxide (5·9 g.) in benzene (100 c.c.), and the ethyl alcohol removed as the binary azeotrope with benzene. After evaporation of the benzene the solid product was heated at 100°/0·1 mm. for several hours to remove excess of *neo*pentyl alcohol (Found: Nb, 17·6%).

Niobium Penta-(1-ethylpropoxide).—Ice-cold pentan-3-ol (diethylcarbinol) (42 g.) was added dropwise to a suspension of the pentachloride (7·0 g.) in frozen benzene (200 c.c.) and the mixture was treated with excess ammonia. The new *alkoxide* was isolated in the usual manner as a red viscous liquid which was distilled (138°/0·1 mm.) and gave a red, chloride-free gelatinous distillate (11·9 g.) (Found: Nb, 17·5%).

Niobium Penta-(1-methylbutoxide).—The pentachloride (8·05 g.), suspended in pyridine (144 g.), was treated with pentan-2-ol (44 g.) and then excess of ammonia. The product remaining after removal of ammonium chloride and solvent was dissolved in benzene and again treated with ammonia and the alcohol. The new *alkoxide* was then isolated as a red liquid which was distilled (123·5°/0·02 mm.) and gave a red chloride-free product (6·84 g.) (Found: Nb, 17·5%).

Niobium Penta-(1 : 2-dimethylpropoxide).—The new *alkoxide* (10 g.) was isolated in the foregoing manner as a pale yellow distillate (b. p. 125°/0·02 mm.) from the reaction involving the pentachloride (5·2 g.), 2-methylbutan-3-ol (methyl*iso*propylcarbinol) (51·8 g.), pyridine (150 c.c.), and ammonia (Found: Nb, 17·6%).

Niobium Penta-(1 : 1-dimethylpropoxide).—(*a*) The pentachloride (9·9 g.) in pyridine (108 g.)

was allowed to react with *tert.*-amyl alcohol (35·8 g.) and excess of ammonia. The viscous product isolated in the usual manner decomposed completely when distillation was attempted (160°/0·7 mm.). (*b*) In another experiment involving the pentachloride (5·38 g.), pyridine (175 c.c.), *tert.*-amyl alcohol (36·4 g.), and ammonia, a dark viscous product (9·8 g.) was isolated at room temperature [Found: Nb, 20·0. $Nb_2O(OC_5H_{11})_8$ requires Nb, 20·7%]. This *product* decomposed during sublimation (120°/0·1 mm.). (Sublimate. Found: Nb, 27·4%.)

Molecular Weights.—These were determined ebullioscopically in benzene by the usual method [1] and the results are given in Table 3.

TABLE 3

R in $Nb(OR)_5$	Range of *m* (g.)	Benzene (g.)	$\Delta T/m$	*M* Found	*M* Calc.
$Me_2CH{\cdot}CH_2$	0·0108—0·1262	15·18	0·231°	840	457·9
MeEtCH	0·0099—0·0500	15·27	0·366	526	,,
$Me_2CH{\cdot}CH_2{\cdot}CH_2$	0·0311—0·1470	13·50	0·228	953	527·9
MeEtCH·CH_2	0·0426—0·2136	15·07	0·200	954	,,
$Me_3C{\cdot}CH_2$	0·0150—0·0582	15·76	0·232	804	,,
Et_2CH	0·0365—0·1492	15·25	0·315	612	,,
$MePr^nCH$	0·0164—0·0844	14·71	0·366	546	,,
$MePr^iCH$	0·0095—0·0476	15·28	0·346	555	,,

We are indebted to Imperial Chemical Industries Limited for a grant for the purchase of the potassium oxyfluoroniobate. One of us (B. N. C.) thanks Bihar University for study leave.

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855. *The Chemical Action of Ultrasonic Waves.*

By A. V. M. PARKE and DUNCAN TAYLOR.

Spectra of the sonoluminescence from aerated bromine water and from aerated aqueous carbon disulphide solution have been examined with a resolution not better than 100 Å. In each case, a broad band in the visible region was detected. For water containing argon, air, oxygen, or nitrogen the intensity of sonoluminescence as measured by a photomultiplier increased with time of irradiation up to equilibrium values which varied linearly with ultrasonic power. Oxidation due to ultrasonic waves increased linearly with time of irradiation in the solutions O_2–H_2O, O_2–KI–H_2O, air–KI–CCl_4–H_2O, A–H_2O, N_2–H_2O, while for the first three the rate of oxidation increased linearly with both ultrasonic power and the intensity of sonoluminescence. For oxygen–water solutions, addition of salts (except potassium iodide) and of sulphuric acid had no effect on the luminescence or oxidation, but for O_2–KI–H_2O solutions a three-fold increase in the rate of liberation of iodine occurred without change in luminescence when the pH was reduced from about 7 to 2. Nuclear hydroxylation of aromatic molecules when irradiated in aqueous solution was observed. The results are discussed in the light of current theories for the action of ultrasonic waves.

NUMEROUS investigations [1-6] of the oxidising action of ultrasonic waves on aqueous solutions have led to the following general conclusions: (*a*) simultaneous occurrence of cavitation and sonoluminescence is essential; (*b*) the action, while more pronounced in presence of dissolved oxygen, also occurs if the dissolved gas is argon, nitrogen, or carbon monoxide; for potassium iodide solutions oxidation is greatly increased by dissolved carbon tetrachloride; (*c*) hydrogen, carbon dioxide, and volatile organic substances such as ether and acetone, but not carbon tetrachloride or carbon disulphide, inhibit the effects. Miller [3] has drawn

[1] Prudhomme and Grabar, *J. Chim. phys.*, 1949, **46**, 318, 323, 667.
[2] Weissler, Cooper, and Snyder, *J. Amer. Chem. Soc.*, 1950, **72**, 1769.
[3] Miller, *Trans. Faraday Soc.*, 1950, **46**, 546; *J. Chim. phys.*, 1951, **48**, 242.
[4] Lindström, *J. Acoust. Soc. Amer.*, 1955, **27**, 654.
[5] Griffing, *J. Chem. Phys.*, 1950, **18**, 997; 1952, **20**, 939.
[6] Griffing and Sette, *ibid.*, 1955, **23**, 503.

attention to the analogy between the chemical effect of ultrasonic waves and that of ionising radiation, and he and other workers [1, 7] have suggested that the oxidising action is "indirect" and consistent with a primary process $H_2O \longrightarrow H + OH$ occurring in the cavities. No direct evidence for the existence of hydroxyl radicals, similar to that of Weiss and his co-workers [8] for ionising radiation, has yet been reported. To account for the primary process, the most widely accepted theory is that of Frenkel,[7] who considers that lens-shaped cavities are oppositely charged on the two faces owing to a non-equilibrium distribution of ions, a subsequent discharge across the cavities being responsible for both the breakdown of water molecules and the sonoluminescence. Prudhomme and Grabar [1] have added that the breakdown may be photochemical provided the luminescence contains a component of sufficiently short wavelength. On the other hand, Noltingk and Neppiras [9] (cf. Griffing [5]) have calculated that during the adiabatic collapse of cavities temperatures of the order of 10,000° may be realised momentarily, thus suggesting thermal dissociation of water and incandescence of gas molecules in the cavities. Marboe's "mechano-chemical" theory [10] involves the breaking of O–H bonds (as distinct from hydrogen bonds) when the liquid water is torn apart during cavitation, and compares sonoluminescence with the ultraviolet luminescence observed by Audubert [11] during the neutralisation of acids and bases.

The following work on the luminescence and chemical effects and their interrelations was undertaken mainly to shed further light on the primary process.

Experimental and Results

Ultrasonic Generator.—This was the Mullard instrument, type E7562, with interchangeable quartz crystals 4·5 cm. in diameter giving frequencies of 0·5, 1, and 2 Mc./sec. A relative measure of the intensity of the ultrasonic beam for a given set of experimental conditions is given by the square of the voltage applied to the crystal. At 0·5 Mc./sec., calorimetric experiments showed a linear relation between the square of the voltage and the heating effect (and thus the intensity) of the ultrasonic beam, and that the range of acoustic power available in the majority of the experiments was 1·2—4·1 w cm.$^{-2}$.

Hydroxylation of Benzoic Acid and Other Aromatic Compounds.—The irradiation vessel (referred to below as vessel I) was a glass tube 6 cm. in diameter, flanged at the lower end and sealed to the face of the transducer head carrying the quartz crystal *via* a thin rubber gasket and brass clamp. The crystal was thus in contact with the solution to be irradiated. Excessive temperature rise was prevented with a glass cooling coil and air was bubbled slowly through the solution during the two-hour irradiation period at maximum power at 0·5 Mc./sec. Saturated benzoic acid solution (50 ml.) was irradiated, concentrated to small volume and filtered, and spots of the filtrate were run on paper chromatograms with a mobile phase of ethanol–water–concentrated ammonia solution (20 : 4 : 1 v/v). The three monohydroxybenzoic acids were chromatographed for comparison, the *ortho*-acid being detected by fluorescence and the *meta*- and *para*-acids by spraying with a solution of *p*-nitrophenylhydrazine which has been treated with nitrous acid as in diazotisation, and exposing to ammonia to give orange spots. The results conclusively showed that all three monohydroxy-acids were formed. A rough estimate of the relative proportions of the three isomers was made by chromatographing spots of the irradiated solution under the same conditions on two separate paper strips. One strip was treated to show the position of the acids, the appropriate areas being cut from the other strip and the acids washed from the paper with water. To each solution were added 2 ml. of a 0·1% solution of 2 : 6-dichloroquinone chloroimide, 0·5 ml. of concentrated ammonia solution, and water to 50 ml., and the resultant coloured solutions were compared in a spectrophotometer with similarly treated known solutions of the three acids. The proportions found were $o > p > m$, and are consistent with a radical substitution process. Good evidence of hydroxylation was also obtained with saturated aqueous solutions of toluene, nitrobenzene, and phenol, but not with benzene.

[7] Frenkel, *Acta Physicochim. U.R.S.S.*, 1940, **12**, 317.
[8] Loebl, Stein, and Weiss, *J.*, 1949, **3241**, 3245, 3256.
[9] Noltingk and Neppiras, *Proc. Phys. Soc.*, 1950, **63**, *B*, 674.
[10] Marboe, *Chem. Eng. News*, 1949, **27**, 2198.
[11] Audubert, *Trans. Faraday Soc.*, 1939, **35**, 197.

Spectrum of Sonoluminescence.—To the dark-adapted eye, sonoluminescence from air-saturated water appears as a faint bluish glow, the intensity of which is increased about six times by addition of bromine or carbon disulphide. Measurements were possible only with the last two solutions. These were contained in a 3 cm.-diameter tube, which was closed with a platinum foil base sealed on with Araldite. The tube was mounted vertically in vessel I, the outer vessel being filled with water to just above the level of the platinum. Luminescence from the solution in the smaller tube passed through a quartz window to the slit of a small Hilger quartz spectrograph. The spectrum was scanned with an E.M.I. eleven-stage photomultiplier, for which full circuit details have been given by Parke.[12] In order to secure a reasonable output from the multiplier, the slits both on the spectrograph and in front of the photocathode of the multiplier were such that the resolution was not better than 100 Å. The useful wavelength range of the multiplier was 3250—6000 Å, maximum sensitivity being at about 4000 Å.

Luminescence from saturated carbon disulphide solution showed a band from about 3700 Å up to the limit of the multiplier's range. The solution itself did not absorb at wavelengths greater than about 3500 Å. Saturated bromine water gave a similar band but the short-wavelength end terminated at about 5200 Å owing to absorption by the solution. The absence of an ultraviolet component was further suggested by the fact that the total luminescence from air-saturated distilled water measured with a photomultiplier sensitive down to 2200 Å showed no change on the addition of sodium salicylate, a solution of which fluoresces when excited by wavelengths in the range 950—3400 Å.[13]

Equipment for Sonoluminescence-intensity and Oxidation-rate Measurements.—Relative luminescence intensities were determined with a nine-stage Mazda photomultiplier and a valve-voltmeter (the multipliers and circuit details[12] were made available by Mr. S. Rodda, Edison-Swan Co. Ltd.). Experiment showed that the response of the instrument was linear with light intensity over the range of intensities encountered.

The transducer head was mounted horizontally in a glass-windowed water thermostat at 20°. In some early experiments on aerated solutions vessel I without the cooling coil was used. Later vessels were constructed either from 42 mm. diameter tubing (vessel II) or from a B40 cone joint (vessel III) and closed at the lower end with a thin glass plate sealed on with Araldite. The plate also served as a flange for clamping the vessel rigidly a few cm. above the crystal. Both the distance from the crystal to the vessel base and the thickness of the base are critical for maximum transmission of ultrasonic energy[9] and were selected by trial, the criterion being maximum luminescence from water in the vessel at a given ultrasonic power. A pump drove a stream of water between the crystal and vessel base to prevent accumulation of air bubbles, which would interfere with the passage of the ultrasonic beam by reflection at the air–water interfaces. The upper end of vessel II was closed with a rubber stopper, carrying gas inlet and outlet tubes and a third tube for withdrawing samples of the irradiated solution. Vessel III was closed with a B40 socket joint fitted with gas inlet and outlet tubes, a third tube dipping to the bottom of the vessel which allowed samples of irradiated solution to be pumped out by gas pressure, and a spoon device let in through a B19 joint so that solid in the spoon could be tipped into the solution at any time without otherwise disturbing the irradiation conditions. Distilled water, redistilled from alkaline potassium permanganate solution and stored in a Pyrex flask, was twice boiled out under vacuum and saturated with the desired gas. The water was pumped by gas pressure to the irradiation vessel, which had been swept out previously by the saturating gas, and admitted through the gas inlet tube. A suitable arrangement of two-way taps between the gas supply, water reservoir, and irradiation vessel allowed either gas or water as required to pass to the vessel. During irradiation, gas was slowly bubbled through or blown over the surface of the solution, both procedures giving very similar results in the measurement of luminescence and of oxidation rate. Cylinder oxygen and " spot " nitrogen (<10 p.p.m. O_2) were used after being passed through liquid-oxygen traps. To remove 0·2% of nitrogen from cylinder argon, the gas was passed over titanium sponge contained in a 26" Mullite tube at 900°, followed by liquid-oxygen traps. The pH of the gas-saturated water was not less than 6·7. All pH values were measured with a Pye glass-electrode meter. In all experiments the photomultiplier was mounted outside the thermostat, with the photocathode about 12 cm. from the irradiation vessel and screened from any luminescence occurring in the thermostat water.

Sonoluminescence Intensity Measurements.—(a) *Dependence on ultrasonic power.* When the generator was first turned on at a given power, gas was expelled from solution by the ultrasonic waves and at the same time the luminescence increased several-fold to an equilibrium value

[12] Parke, Thesis, Edinburgh, 1955.
[13] Miller and Brown, *Trans. Faraday Soc.*, 1955, **51**, 1623.

(with uncontrollable random fluctuations of ±10%) after 1—3 min. depending on the power and the nature of the dissolved gas. These equilibrium values were regarded as characteristic of the power applied, and were found to increase linearly with power in all cases. Relative intensities at maximum power and 0·5 Mc./sec. were 1, 1, 2·2, and 8·4 for oxygen, nitrogen, air, and argon respectively, and 12 for both bromine water and carbon disulphide solution when they were left exposed to the atmosphere during irradiation with no gas bubbling through the solution. The results also suggested a power threshold below which no luminescence occurred.

(b) *Dependence on temperature.* For air-saturated water in vessel I, the luminescence at maximum power and frequencies of 0·5 and 1 Mc./sec. decreased linearly with rise in temperature over the range 5—50°. In any experiment to determine luminescence or oxidation effects the passage of the ultrasonic beam inevitably caused a rise of not more than 3°. The fall in luminescence so caused could not be greater, however, than the 10% fluctuation in the measurement.

(c) *Dependence on concentration of dissolved oxygen.* Vessel II was used except that a 25 ml. pipette fitted with taps at each end of the bulb was inserted in place of the sampling tube. With maximum power at 0·5 Mc./sec. oxygen-saturated water was irradiated with no gas flowing until the luminescence rose to a predetermined value, after which the generator was switched off and the water immediately sampled by applying very gentle suction to the pipette. The oxygen concentration was measured by Winkler's method,[14] the iodine liberated being determined by absorption at 3530 Å. The small amount of hydrogen peroxide produced during irradiation, which also liberated iodine, was corrected for by being determined in a second sample of water by Ovenston and Rees's method.[15] As the oxygen concentration decreased from 100% to about 45% of the saturation value the luminescence rose approximately six-fold, the effect requiring 2—3 min. irradiation. Longer irradiation caused a small further rise in luminescence with very little change in the oxygen concentration. This further rise did not occur if oxygen was passed through or over the water during irradiation; instead the equilibrium luminescence value mentioned above was established.

(d) *Dependence on* pH *and the presence of dissolved salts.* The equilibrium luminescence value for an oxygen–water solution at 0·5 Mc./sec. in vessel II having first been determined, sulphuric acid to reduce the pH of the water to about 2 or a salt (KCl, KNO_3, K_2SO_4, KH_2PO_4) to give a 0·2M-solution was added through the sampling tube. On re-irradiation at the same power, no significant change in the luminescence was observed in any case.

Irradiation of Oxygen–Water Solutions.—In vessel II, 120 ml. of oxygen-saturated water were irradiated at a given power at 0·5 Mc./sec. for six successive periods of 2—4 min. each, a 2 ml. sample being withdrawn after each period and the hydrogen peroxide determined by Ovenston and Rees's method.[15] Experiment showed that the small change in volume due to the removal of samples had no significant effect on the rate of peroxide formation. Typical results for four different powers are shown in Fig. 1. The slow initial rates of peroxide formation are undoubtedly connected with the expulsion of oxygen from the water, subsequent establishment of equilibrium luminescence leading to higher and constant rates. A linear relation between the constant rates and relative power is suggested by Fig. 2.

The relation between equilibrium luminescence and rate of peroxide formation was determined by using solutions which had been pre-irradiated at a suitable power until a predetermined luminescence had been established. The quantity of peroxide produced during the pre-irradiation was subtracted from that found in the successive samples, thus eliminating the effect of the early slow rate. The concentration of peroxide was then found to increase linearly with time (Fig. 3). The rate–luminescence graph (Fig. 2) shows a slight curvature, but in view of the errors in the measurement of luminescence intensity (±10%) and in the calculation of rates (±5%), the apparent departure from linearity may not be significant. Fig. 2 also indicates a low-power threshold below which no peroxide is formed and the absence of peroxide at zero luminescence.

To determine the effect of salts and of sulphuric acid on the rate of peroxide formation at a given luminescence, a "split-run" procedure was adopted. After the desired luminescence was established, irradiation was continued for 3 successive periods of 2, 2, and 4 min. each respectively; the salt (0·2M-KCl, -KNO_3, -K_2SO_4, -KH_2PO_4) or acid (to give pH about 2) was then added through the sampling tube and the irradiation continued for 2 periods of 4 min. each. In no case did the addition of salt or acid cause any significant change in the gradient of the linear peroxide concentration–time graphs.

[14] Winkler, *Ber.*, 1888, **21**, 2843; Bairstow, Francis, and Wyatt, *Analyst*, 1947, **72**, 340.
[15] Ovenston and Rees, *Analyst*, 1950, **75**, 204.

During the above experiments, reproducibility was better when irradiation was controlled with reference to equilibrium luminescence rather than power. The former control was adopted therefore in a number of the experiments reported below.

Irradiation of Nitrogen–Water Solutions.—In vessel III and with a frequency of 0·5 Mc./sec., 70 ml. of nitrogen-saturated water were irradiated at maximum luminescence for 5 successive periods of 10 min. each. After each period, 5 ml. were withdrawn for nitrite-ion determination

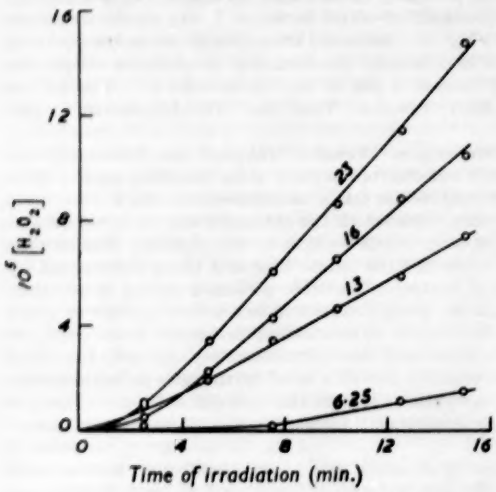


FIG. 1. *Formation of H_2O_2 at constant ultrasonic power in O_2–H_2O solutions. The numerals on the curves represent relative power.*

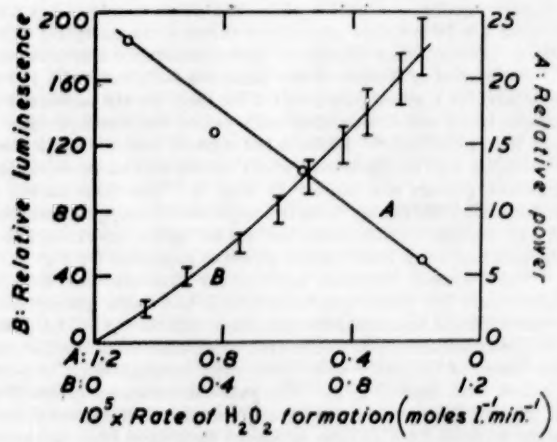


FIG. 2. *Rate of H_2O_2 formation in O_2–H_2O solutions as a function of ultrasonic power (A) and sonoluminescence (B).*

by Rider and Mellon's method,[16] and 5 ml. of fresh nitrogen-saturated water added to restore the original volume. Due allowance was made in the analysis figures for the successive dilutions. While the concentration of nitrite ion was found to increase linearly with time of irradiation, the rate (about 10^{-6} moles $l.^{-1}$ $min.^{-1}$) varied considerably from one experiment to another. At the end of the runs the nitrate ion concentration, obtained by Woodward's method [17] with a probable error of $\pm 10\%$, was approximately half that of the nitrite. The ratio nitrate : nitrite did not change significantly on allowing the solution to stand for periods up to 1 hr. after irradiation either in the air or under nitrogen. If before irradiation the pH of

[16] Rider and Mellon, *Ind. Eng. Chem. Anal.*, 1946, **18**, 96.
[17] Woodward, *Analyst*, 1953, **78**, 727.

the water was raised to 8 or 10 by addition of sodium hydroxide, no significant change was observed in the nitrate or nitrite ion concentrations at the end of the run compared with those observed in neutral solutions; at pH 2 the ratio nitrate : nitrite in the irradiated liquid rose to 5, but the sum of the concentrations of the two ions remained unchanged.

Since Ovenston and Rees's method [15] for hydrogen peroxide was unsatisfactory in presence of nitrite ion an estimate of the peroxide formed in neutral solutions was obtained as follows.

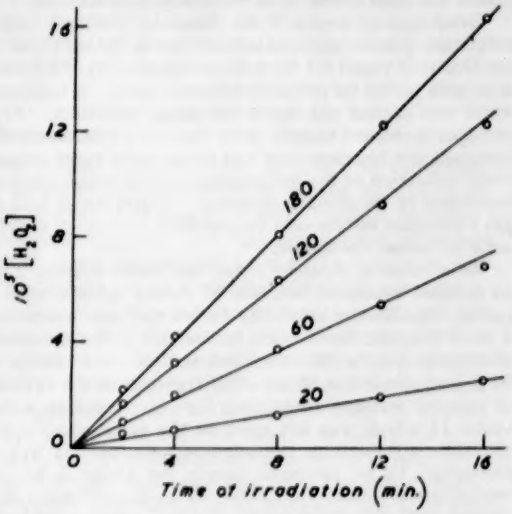


FIG. 3. *Formation of H_2O_2 at constant sonoluminescence in O_2–H_2O solutions. The numerals on the lines represent relative luminescence intensity.*

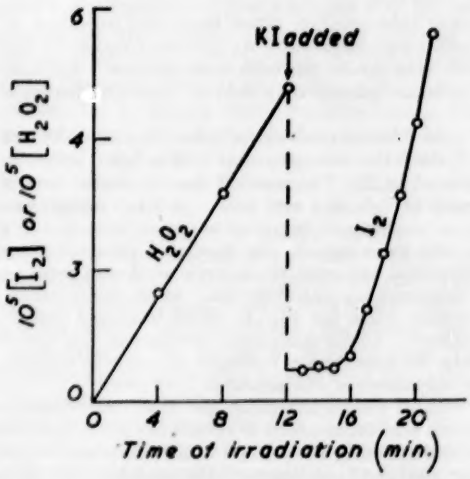


FIG. 4. *Irradiation of KI–H_2O_2–H_2O solutions.*

After determination of the nitrite, an equal volume of 2N-sulphuric acid and a known excess of sodium nitrite were added to a fresh portion of the solution, which was kept for 1 hr. before the residual nitrite was determined. Under such conditions, experiments with known mixtures of sodium nitrite and hydrogen peroxide showed that about 90% of the peroxide reacted, reproducibility being not better than ±20%. Within these limits, the peroxide and nitrite concentrations were found to be the same at the end of the runs. (The more satisfactory method of Schwarz and Allen [18] was published after this work was completed.)

[18] Schwarz and Allen, *J. Amer. Chem. Soc.*, 1955, **77**, 1324.

The presence of ammonium ions at the end of the runs was confirmed by Nessler's reagent, the concentration being about the same as that of nitrite or peroxide. Tests for hydrazine were negative.

In the same vessel with the same luminescence, but with irradiation periods of 2·5 min., experiments with oxygen–water solutions showed the rate of hydrogen peroxide formation to be more reproducible and 10—15 times faster than that of nitrite ion, and 3—4 times faster than that of the total products, in the nitrogen–water case.

Irradiation of Argon–Water Solutions.—With a frequency of 0·5 Mc./sec. at approximately maximum power, argon-saturated water (70 ml.) was irradiated under constant luminescence conditions in vessel III for 5 successive periods of 2·5 min. each, a 2 ml. sample being withdrawn after each period for peroxide determination. A comparative experiment with oxygen-saturated water was carried out under the same conditions. For argon solutions, the concentration of peroxide increased linearly with time at a rate about 20% less than that for oxygen solutions, although the luminescence was some eight times greater. Within the limits of experimental error, reduction of the luminescence of the argon solutions by half reduced the rate of peroxide formation in the same proportion. Argon which had not been purified with titanium at 900° gave the same results, and no nitrite or nitrate ion could be detected in solution after irradiation with full power for 25 min.

Irradiation of Aqueous Potassium Iodide–Carbon Tetrachloride Solutions in Air.—250 ml. of an aerated saturated solution of carbon tetrachloride in water containing 2 g. of potassium iodide, dissolved immediately before use, was irradiated at a given power and a frequency of 1 or 2 Mc./sec. for 1 min. in vessel I. The luminescence fell during irradiation owing to absorption by the liberated iodine, but an arbitrary value (estimated to be not more than 20% low) was taken 15 sec. after the start of the irradiation. Similar irradiations with 100 ml. of aerated solution containing 1 g. of potassium iodide were carried out at 0·5 Mc./sec. in vessel II which was left open to the atmosphere. The iodine liberated was determined by titration with sodium thiosulphate solution. It was observed that small amounts of iodine continued to be liberated slowly for about 2 hr. after the irradiation, and that results reproducible within $\pm 5\%$ were obtained only when the final end-points in the titrations were determined after this period. Experiment showed that the concentration of potassium iodide used was three times greater than the threshold concentration below which the liberation of iodine becomes dependent on the potassium iodide concentration. At all three frequencies the rate of iodine formation increased linearly both with power and with luminescence. The rate with full power at 0·5 Mc./sec. was about 70 times greater than that of hydrogen peroxide formation in oxygen–water solutions.

Irradiation of Potassium Iodide–Water–Oxygen Solutions.—Solid potassium iodide sufficient to give a 0·1M-solution was added to vessel II, the latter was swept out with oxygen, and then 120 ml. oxygen–saturated water were transferred to it. The solution was irradiated with a constant power at 0·5 Mc./sec. for six successive periods of 1 min. each. A 2 ml. sample was withdrawn after each period and the iodine determined by absorption at 3530 Å. The luminescence increased gradually during the first three periods and reached a constant value during the last three. As the rate of iodine liberation was many times less than that in presence of carbon tetrachloride, no significant fall in luminescence was observed. At all power values, the rate of oxidation ultimately reached a steady value (cf. Fig. 1) which increased linearly with both power and the intensity of luminescence. Under comparable conditions, the rate of iodine liberation was about 1·3 times faster than the formation of hydrogen peroxide in oxygen–water solutions, although the intensity of the luminescence was similar in both cases.

To determine the effect of pH on the rate of iodine liberation the split-run procedure described above was adopted, sufficient sulphuric acid being added to reduce the pH to between 1·35 and 2·90. Changes in the extent of the absorption at 3530 Å due to the alterations in pH were allowed for in the analyses. In all cases change of pH increased the oxidation rate by a factor of nearly three without causing any significant change in the luminescence.

If after irradiation the samples were allowed to stand, no further increase in the iodine concentration occurred. On the other hand, when oxygen-saturated water was irradiated at full power for 5 min. and then mixed with an equal volume of 0·2M-potassium iodide, the hydrogen peroxide formed during irradiation required 2 hr. to react completely with the potassium iodide, a first-order kinetic law being observed. The liberation of iodine by irradiation evidently does not proceed *via* the intermediate formation of hydrogen peroxide. The possibility remains that the normal peroxide–iodide reaction may be catalysed in some way by the ultrasonic beam. To examine this, oxygen-saturated water was irradiated at constant

luminescence for three successive periods of 4 min. each, the peroxide formed being determined after each period. Solid potassium iodide was then added to make the solution 0·1M, and the irradiation continued at the same luminescence for nine successive periods of 1 min. each, the iodine liberated being measured after each minute. Typical results are shown in Fig. 4. In that part of the experiment after the addition of potassium iodide no increase in the iodine concentration of the successive samples occurred if the samples were allowed to stand for 30 min., or if the ammonium molybdate catalyst of Ovenston and Rees's method [18] was added and the sample kept for 5 min. Under irradiation, therefore, virtually all the hydrogen peroxide originally formed was destroyed, but with the liberation of only a very small amount of iodine, in 1—2 min. after the addition of potassium iodide.

Discussion

Primary Process and Sonoluminescence.—The hydroxylation of aromatic molecules observed during irradiation in aqueous solution provides evidence for the formation of hydroxyl radicals and supports a primary process $H_2O \longrightarrow H + OH$. Failure to detect an ultraviolet component in the luminescence suggests that the breakdown of water molecules is not photochemical, and that sonoluminescence is not the same as the luminescence observed by Audubert.[11] Since there are no permitted electronic transitions in the water molecule that could give rise to the observed luminescence in the visible region,[13] and since the intensity was found to vary with the nature and concentration of the gas present, it seems that the light must come from excited molecules other than water. According to Frenkel's theory,[7] the intensity of the electric discharge across the cavities, and therefore the luminescence, would be expected to vary with the concentration of ions in solution. Approximate calculations have shown that addition of salts or sulphuric acid in the amounts used should have increased the cavity potentials by a factor of at least ten, yet no significant change in luminescence intensity was observed. On the other hand, increase in luminescence with increase in power and variation of luminescence with the nature and concentration of the dissolved gas are qualitatively in agreement with the theory. Furthermore, the relative luminescence order argon solutions > air solutions > nitrogen solutions is the same as the order of the first Townsend ionisation coefficients [20] for the three gases, if the coefficients are estimated by assuming potentials of the order given by Frenkel.[7] However, for hydrogen where luminescence is zero, the coefficient estimated from data given by Rose *et al.*[21] is greater than that for air.

Frenkel [7] and others have suggested an analogy between the electric potential across the ultrasonic cavities and Thomson's " ballo-electric " potential [22] on the surface of newly formed water droplets. The low value of the potential when the drops are formed in an atmosphere of hydrogen is compared with the absence of luminescence and oxidative effects in solutions irradiated in presence of hydrogen. However, Thomson also reported a fall in potential when the water from which the drops were formed in air contained sulphuric acid or potassium iodide, both of which have been shown not to reduce the luminescence or oxidation effects. In view of this, the analogy does not appear to be satisfactory.

According to the theory of Noltingk and Neppiras [9] the temperatures due to the adiabatic collapse of cavities depend upon the ratio of the specific heats of the gases present in the cavities. Luminescence being assumed to increase with temperature, the predicted luminescence order would be $A > O_2 = N_2 > Br_2 > CS_2$ whereas the observed order was $Br_2 = CS_2 > A > O_2 = N_2$. Their theory, however, does not require the luminescence to vary with the concentration of ions in solution, and in other respects appears to be not less satisfactory than Frenkel's theory. The suggested cavity temperatures of about 10,000° correspond to an energy of only about 1 ev, but a Boltzmann distribution of energies being assumed, a small fraction of the water molecules would possess sufficient energy for dissociation.

[18] Dewhurst, *Trans. Faraday Soc.*, 1953, **49**, 1174.
[20] Loeb, " Fundamental Processes of Electrical Discharges in Gases," Wiley and Sons Inc., New York, 1947, p. 342.
[21] Rose, De Bitetto, and Fisher, *Nature*, 1956, **177**, 945.
[22] Thomson, *Phil. Mag.*, 1894, **37**, 341.

Griffing and Sette [6] have reported non-linear relations between luminescence and power for aqueous solutions of carbon tetrachloride containing argon or carbon monoxide and for undistilled water containing air. The departures from linearity are most marked at powers greater than those used in the present work, and it is doubtful if their luminescence values are strictly comparable with the equilibrium values discussed above.

Chemical Effects.—Water with dissolved oxygen, argon, and nitrogen. Granted a primary process $H_2O \longrightarrow H + OH$ increasing linearly with power and with luminescence in any given solution, the observed linearities in the oxidation results are understandable. However, since the overall chemical activity in solution at the same power is in the order $O_2 > A > N_2$, in spite of the much higher luminescence with argon, and since oxidation and reduction of nitrogen occur, other reactions, in addition to $H_2O \longrightarrow H + OH$ with the subsequent formation of hydrogen peroxide and the very small amounts of hydrogen and oxygen reported by Prudhomme and Grabar,[1] must occur. The higher activity in presence of oxygen could be due to the reaction $H + O_2 \longrightarrow HO_2$, which would be absent with argon and nitrogen, and possibly to the activation of oxygen molecules in or on the ultrasonic cavities (cf. Bresler [23]). Activation of gas molecules is also suggested by the high luminescence in argon solutions without a correspondingly high yield of hydrogen peroxide. The formation, in nitrogen-containing solutions, of nitrite, nitrate, and ammonium ions, in addition to hydrogen peroxide, suggests interaction between H and OH and normal or excited nitrogen molecules. Increase in the ion ratio nitrate : nitrite without change in the total yield of these ions as the pH is reduced is considered to be due to the oxidising action of the hydrogen peroxide in acid solution (cf. Virtanen and Ellfolk [24]).

Potassium iodide solutions. The much higher rate of iodine liberation without notable change in luminescence when potassium iodide solutions are irradiated in presence of carbon tetrachloride, and the fact that the latter is destroyed during irradiation,[2, 6] suggest either that recombination of H and OH is reduced by their reaction with carbon tetrachloride to produce chlorine, or that carbon tetrachloride is dissociated during cavitation. The small amount of iodine liberated after the end of the irradiation could be due to reaction of iodide ions either with oxidation products of carbon tetrachloride or with traces of nitrite.

In the absence of carbon tetrachloride the three-fold increase in the rate of iodine liberation on reducing the pH from about 7 to 2 may be due to the equilibrium reaction [25] $HO_2 \rightleftharpoons H^+ + O_2^-$. On this basis, however, pH would be expected to affect the rate of peroxide formation in oxygen–water solutions, but this was not observed. The slow liberation of iodine by very low concentrations of hydrogen peroxide, in contrast to its immediate liberation by irradiation, and the absence of any post-irradiation reaction, show that hydrogen peroxide is not an intermediate in the ultrasonic reaction in 0·1M-solution. This view is supported by the surprisingly rapid destruction of peroxide with the liberation of much less than an equivalent amount of iodine when the former in low concentration was irradiated in presence of the iodide. Since other salts and sulphuric acid had no effect on the rate of peroxide formation in oxygen–water solutions, the destruction evidently involves the iodide ion. Some of Lindström's results [4] suggest a similar destruction of peroxide, and he considered that iodine in equivalent quantity was in fact formed but subsequently lost from solution by the de-gassing action of the ultrasonic waves. Loss of iodine in this way was never observed in the present work. Lindström has also reported the formation of both iodine and hydrogen peroxide when 0·0004M-potassium iodide was irradiated at pH 4. This, however, could well be due to the concentration 0·0004M being less than the threshold concentration,[2] below which the rate of oxidation becomes dependent on the iodide concentration : some of the hydroxyl radicals or activated oxygen molecules could then interact to give peroxide before encountering iodide ions.

Grateful acknowledgments are due to Dr. N. Miller for valuable discussions.

CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH. [*Received, July 13th*, 1956.]

[23] Bresler, *Acta Physicochim. U.R.S.S.*, 1940, **12**, 323.
[24] Virtanen and Ellfolk, *Acta Chem. Scand.*, 1950, **4**, 93.
[25] Donaldson and Miller, *Trans. Faraday Soc.*, 1956, **52**, 652.

856. *Curare and Related Topics. Part II.* The Structure and Anomalous Optical Rotation of* iso*Chondrodendrine.*

By JOHN A. D. JEFFREYS.

Fission of *iso*chondrodendrine diethyl ether with sodium in liquid ammonia gave only (−)-1 : 2 : 3 : 4-tetrahydro-7-ethoxy-1-4′-hydroxybenzyl-6-methoxy-2-methyl*iso*quinoline (IId), proving the structure of *iso*chondrodendrine to be (Ia). The specific rotation of *iso*chondrodendrine in excess of acid varies markedly with the concentrations of acid and base.

*iso*CHONDRODENDRINE, one of the chief alkaloids of the South American *Chondrodendron* species, was shown to have structure (Ia or b) by Faltis [1] and by King; [2] fission of the dimethyl ether (cycleanine) with sodium in liquid ammonia [3,4,5] to give (−)-armepavine (IIa) as the product showed that both optically active centres had the same sign of rotation. The position of one of the hydroxyl groups remained uncertain. King [2] had shown, using the Millon reaction, that one of the hydroxyl groups had a vicinal substituent on each side of it, and Faltis [1] had assumed that the molecule was symmetrical since it could then arise from two molecules of coclaurine (IIb). This is not a conclusive argument; *iso*chondrodendrine occurs in both *Chondrodendron tomentosum* and *Ch. platyphyllum*: the former yields also chondrocurine (IVa),[6] and the latter chondrofoline (IVb),[2] each of which contains an *iso*coclaurine (IIc) nucleus.

(I) a: R = Me, R′ = H
b: R = H, R′ = Me

(II)

	R	R′	R″
a:	Me	Me	Me
b:	H	Me	H
c:	H	H	Me
d:	Me	Me	Et
e:	Me	Et	Me

(III)

(IV) a: R = Me, R′ = H, R″ = Me, R‴ = H
(IV) b: R = H, R′ = H or Me, R″ = Me or H, R‴ = Me

(V) R = Me or Et, R′ = Et or Me, R″ = CH_2Ph, R‴ = H

(VI) Me Me Me OMe

* Part I, *J.*, 1954, 159.

[1] Review: Kulka, "The Alkaloids," Ed. Manske and Holmes, Academic Press Inc., New York, 1954, Vol. IV, pp. 224 *et seq.*
[2] King, *J.*, 1940, 737.
[3] Tomita, Fujita, and Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 301; *Chem. Abs.*, 1952, **46**, 4555.
[4] Fujita and Murai, *ibid.*, p. 1043; *Chem. Abs.*, 1952, **46**, 5061.
[5] Kidd and Walker, *J.*, 1954, 669.
[6] Dutcher, *J. Amer. Chem. Soc.*, 1946, **68**, 419.

Accordingly, *iso*chondrodendrine was treated with diazoethane, and the resulting diethyl ether split with sodium in liquid ammonia. The sole phenolic product was identical with a synthetic sample of (−)-7-ethoxy-1 : 2 : 3 : 4-tetrahydro-1-4′-hydroxybenzyl-6-methoxy-2-methyl*iso*quinoline (IId), proving the truth of Faltis's original assumption that *iso*chondrodendrine has structure (Ia).

The synthesis of the two possible fission products (IId and e) followed in general a standard route. Schlittler's method [7] for converting *O*-ethylvanillin and *O*-ethyl*iso*vanillin into the corresponding phenethylamines has been improved, and these bases were converted into the required amides (V) by heating them with the diazo-ketone (III) in an inert solvent. The amide (VI) has been synthesised by Eistert [8] in this way, though no experimental details are available, and similarly some anilides have been prepared by Baddeley, Holt, and Kenner.[9] In the examples described in the Experimental section, the water produced in the reaction presumably arose by condensation of the amine with the carbonyl group of the diazo-ketone, before the latter had had time to become the keten.

Resolution of the two bases (IId and e) presented no difficulty, malic acid being successful with the former, and quinic acid with the latter; in the second case, only the (−)-isomer was obtained pure. The two (−)-bases had different melting points and optical rotations in chloroform; their infrared spectra differed but did not permit a clear distinction between the possibilities that *iso*chondrodendrine diethyl ether would give two molecules of (IId), or one each of (IId) and (IIe); paper chromatography did not separate the two isomers. Both the lævorotatory ethers gave a lævorotatory product on de-*O*-alkylation, showing that interchange of methoxy- and ethoxy-groups at positions 6 and 7 did not change the sign of the active centre.

The Optical Rotation of iso*Chondrodendrine.*—A new base with $[\alpha]_D$ +127° (*c* 0·2 in N-sulphuric acid) was found in the mother-liquors of the *iso*chondrodendrine isolated for this work. As this value for $[\alpha]$ is within the range recorded for *iso*chondrodendrine,[5,10,11] the specific rotation of the latter was examined. It was found to be anomalous.

The specific rotation of *iso*chondrodendrine in excess of acid varied markedly with the temperature and with the concentrations of acid and base. Over the concentration range $c = 0{\cdot}2$—$1{\cdot}3$, at 20°, the specific rotation in N-sulphuric acid is given by the equation $[\alpha]_D^{20} = 203° - 12°/c$, where *c* is the concentration in g./100 c.c. (see Table), the temperature variation being described roughly by the equation $d[\alpha]/dT = [\alpha]/70 - 4{\cdot}2$. After readings 2—5, 9, and 10 had been taken, the base was recovered and recycled, then giving readings 1, 6, 8, and 11, showing that this variation is not due to decomposition of the base.

No.:	1	2	3	4	5	6	7	8	9	10	11
c	1·293	1·088	0·817	0·546	0·273	0·215	0·137	0·108	0·068	0·034	0·0108
$[\alpha]$ (found) ...	+194°	+192°	+189°	+178°	+160°	+148°	+128°	+116°	+95°	+50°	(0)
$[\alpha]$ (calc.)	+194°	+192°	+188°	+181°	+159°	+147°	+115°				
Found in 0·1N-H_2SO_4:		*c*	0·841	0·084							
		$[\alpha]$	+164°	+73°							

Ionic association seems the probable cause of this variation and, by making simplifying assumptions, it is possible to obtain a measure of the degree of association, as follows. Assume the solution to contain $(1 - x)c_1$ mole of monomer, with specific rotation $[\alpha_1]$, in equilibrium with x/nc_1 mole of polymer containing *n* units and having specific rotation $[\alpha_2]$, c_1 being in mole per l. Then,

$$\frac{xc_1}{n} \cdot \frac{1}{(1-x)^n} \cdot c_1^n = K_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Changing c_1 into *c*, expressed in g. per 100 c.c., changing the constant, and rearranging the equation gives:

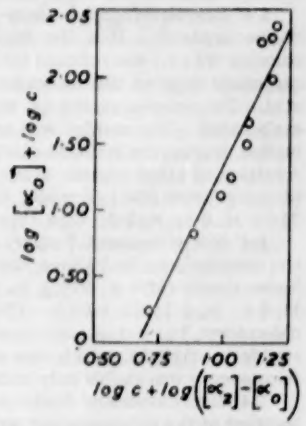
$$c^{n-1} = (x/n) \,.\, [1/(1-x)^n] \,.\, (1/K) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

[7] Schlittler, *Ber.*, 1933, **66**, 992.
[8] Eistert, *Angew. Chem.*, 1941, **54**, 124; Bachmann and Struve, "Organic Reactions," Ed. Adams, John Wiley and Sons Inc., New York, 1942, Vol. I, p. 44.
[9] Baddeley, Holt, and Kenner, *Nature*, 1949, **163**, 766.
[10] King, *J.*, 1948, 1945.
[11] McKennis, Hearst, Drisko, Roe, and Alumbaugh, *J. Amer. Chem. Soc.*, 1956, **78**, 248.

If $[\alpha_1]$ is taken as the zero for specific rotations, $x = [\alpha_o]/[\alpha_2]$, where $[\alpha_o]$ is the observed specific rotation. Substituting this value for x into equation (1*a*), taking logarithms, and rearranging gives:

$$n\{\log c + \log([\alpha_2] - [\alpha_o])\} = \log [\alpha_o] + \log c + \text{Constant} \quad . \quad . \quad . \quad (2)$$

A plot of $\{\log [\alpha_o] + \log c\}$ against $\{\log([\alpha_2] - [\alpha_o]) + \log c\}$ should give a straight line of slope n. If $[\alpha_1]$ is taken as 0°, and $[\alpha_2]$ as +206°, the points fit fairly well on a straight line of slope 4 (see Figure), but, as $[\alpha_1]$ is rather uncertain, this should be taken as an order of magnitude only.



The equation $[\alpha]_D^{20} = +203° - 12°/c$ (see above) implies that $[\alpha_2] = +203°$; however, this equation was intended to hold over as great a concentration range as possible. Extrapolation for $[\alpha_2]$ based on the values of $[\alpha_o]$ in the four most concentrated solutions gives +206° as a better value.

(I am grateful to one of my referees for suggesting the development, quoted above, to give n by a graphical in place of a computational method.)

Compounds (IId and e) have been examined by Mr. J. J. Lewis, of the Department of Materia Medica, Glasgow University, who reports that they have a very weak curare-like activity on isolated tissues, but are convulsant poisons for intact animals. Details will be reported elsewhere.

Experimental

iso*Chondrodendrine*.—This base was isolated as described in Part I. A moving-film evaporator was used to concentrate the intensely foaming extract of the wood; without this apparatus, the isolation becomes tedious. *Chondrodendron limaciifolium* (1100 g.) gave *ca.* 2 g. of crude base which was recrystallised, first by adding methanol to its solution in chloroform, then from methanol alone. The alkaloid then appeared as needles, m. p. 288° (decomp.), $[\alpha]_D^{20}$ (in $CHCl_3$) −29° (*c* 1·3), −31° (*c* 0·33). With diazomethane it gave the dimethyl ether, m. p. 270—271° (decomp.; rapid heating), $[\alpha]_D^{19}$ −34° (*c* 0·3 in MeOH). Evaporation to dryness of solutions of this sample of *iso*chondrodendrine in dilute sulphuric acid disclosed traces of another base (probably base A, cf. Part I) whose sulphate crystallised in long thin plates (cf. Part I).

3-Ethoxy-4-methoxy- and 4-Ethoxy-3-methoxy-phenethylamine.—These were prepared from *O*-ethyl*iso*vanillin and *O*-ethylvanillin respectively by Schlittler's method,[7] the required amides being made by heating the corresponding acids with 1 mol. of urea at 200—220° for 4 hr.[12] The product was dissolved in chloroform and washed with sodium carbonate solution. After removal of the chloroform, the residue was recrystallised from benzene, in which the amides were sparingly soluble (yield 70—80%).

p-*Benzyloxyphenyl Diazomethyl Ketone* (III).—*p*-Benzyloxybenzoyl chloride (5·2 g., 1 mol.) in dry benzene (50 c.c.) was added to ether (200 c.c.) containing diazomethane (2·6 g., 3 mols.). After 24 hr. at room temperature the liquid was decanted from the crystals that had separated, and concentrated to *ca.* 50 c.c. Several hours later a second crop of crystals was collected. The *diazo-ketone* (3·96 g., 74%) formed pale yellow plates, m. p. 117° (decomp.), very soluble in benzene. For analysis a sample was precipitated from benzene solution with light petroleum (b. p. 60—80°) (Found: C, 71·7; H, 4·5; N, 10·9. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·7; N, 11·2%).

p-*Benzyloxy*-N-(*3-ethoxy-4-methoxyphenethyl*)*phenylacetamide*.—A solution of the above ketone (9·8 g., 1 mol.) and 3-ethoxy-4-methoxyphenethylamine (7·4 g., 1 mol.) in warm dry dichlorotoluene (b. p. 192—200°) (100 c.c.) was added dropwise during 30 min. to boiling dichlorotoluene (20 c.c.). The solution became deep red, and water collected in the condenser. Refluxing was continued for 10 min. after the addition, and the solution left for 24 hr. at room temperature. The crude product that had separated was collected (10·8 g.), and a further 0·5 g. was obtained by removal of the solvent in steam and repeated extraction of the dried residue with boiling light petroleum (b. p. 80—100°); recrystallisation of the crude product (73%)

[12] Cherbuliez and Landolt, *Helv. Chim. Acta*, 1946, **29**, 3509.

from benzene gave the *amide* as needles, m. p. 125° after sintering from 121° (Found: C, 74·6; H, 7·0; N, 3·6. $C_{26}H_{29}O_4N$ requires C, 74·5; H, 6·9; N, 3·3%).

p-Benzyloxy-N-(4-ethoxy-3-methoxyphenethyl)phenylacetamide.—The diazoketone (15·4 g.) and 4-ethoxy-3-methoxyphenethylamine (11·4 g.) in dichlorotoluene (120 c.c.) gave, as above, the *amide* (16·8 g., 69%) as needles, m. p. 113° (from benzene) (Found: C, 74·7; H, 6·9; N, 3·3%). In some runs of the two experiments described above, the solid diazo-ketone (1 mol.) was added at *ca.* 0·2 g./min., to a solution of the amine (1 mol.) in boiling decalin. The yield was the same, and was not improved by the presence of suspended silver oxide. Increasing the rate of addition of the diazo-ketone reduced the yield.

1-4′-*Benzyloxybenzyl*-6-*ethoxy*-3 : 4-*dihydro*-7-*methoxy*isoquinolinium *Chloride*.—A solution of the amide (V; R = Me, R′ = Et) (11·3 g.) in chloroform (100 c.c.) and phosphorus oxychloride (20 c.c.) was refluxed for 4 hr. After cooling, the chloroform was extracted with sodium carbonate solution till the washings remained alkaline to litmus, then with dilute hydrochloric acid. To remove excess of water the chloroform solution was filtered, and the solvent evaporated. The residue was extracted with boiling benzene, which removed some colouring matter, leaving the *hydrochloride* (10·1 g., 93%), m. p. 214° (decomp., varies with rate of heating). Addition of ethyl acetate to its solution in chloroform gave minute needles, m. p. 213—215° (decomp. from 200°) (Found: C, 71·1; H, 6·6; N, 3·4; Cl, 8·3. $C_{26}H_{27}O_3N$,HCl requires C, 71·3; H, 6·4; N, 3·2; Cl, 8·1%).

1-4′-*Benzyloxybenzyl*-7-*ethoxy*-3 : 4-*dihydro*-6-*methoxy*isoquinolinium *Chloride*.—Treated in the manner described above, the amide (V; R = Me, R′ = Et) (16·8 g.) gave the crude *amine hydrochloride* (17·0 g., 97%), m. p. 203° (effervescence, shrinking from 140°) (Found: C, 71·4; H, 6·6; N, 3·7; Cl, 8·4%). This salt, and the isomer, were readily soluble in methanol and in chloroform, but not in cold water. Each possessed in the solid state a vivid blue fluorescence, visible in daylight, which was similar in colour to that of pure anthracene; in solution the fluorescence was visible only under ultraviolet illumination.

1-4′-*Benzyloxybenzyl*-6-*ethoxy*-3 : 4-*dihydro*-7-*methoxy*-2-*methyl*isoquinolinium *Iodide*.—To a solution of the corresponding tertiary amine hydrochloride (6·97 g.) in methanol (80 c.c.) under nitrogen, a solution of sodium methoxide (from 0·4 g. of the metal) in methanol (20 c.c.) was added, followed by methyl iodide (13 c.c.), and the solution was refluxed for 6 hr. Evaporation left yellow crystals which were taken up in chloroform and washed with water, and the solvent was evaporated. Recrystallisation from methanol gave the quaternary *salt* (6·2 g., 71%) as yellow prisms, m. p. 209—211° (decomp. from 170°), with a golden-yellow fluorescence under ultraviolet light. A further recrystallisation from methanol did not alter the m. p. (Found: C, 59·5; H, 5·8; N, 3·1; I, 23·2. $C_{27}H_{30}O_3NI$ requires C, 59·7; H, 5·5; N, 2·6; I, 23·4%). In solution this salt was very readily oxidised.

1-4′-*Hydroxybenzyl*-6-*ethoxy*-1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline*.—The methiodide described above was debenzylated and reduced as described by Kidd and Walker,[5] giving the tertiary *amine* (IIe) (42%). Recrystallisation from toluene gave prisms, m.p. 124—125° (Found: C, 73·5; H, 7·4; N, 4·6. $C_{20}H_{23}O_3N$ requires C, 73·4; H, 7·7; N, 4·2%). In a later run without isolation of the intermediate compounds, the dihydro*iso*quinoline hydrochloride (10·1 g.) gave this base (6·3 g., 84%).

1-4′-*Hydroxybenzyl*-7-*ethoxy*-1 : 2 : 3 : 4-*tetrahydro*-6-*methoxy*-2-*methyl*isoquinoline.—The corresponding dihydro*iso*quinoline hydrochloride (6·94 g.) was converted, as in the preceding experiment, *via* the methiodide (which did not crystallise) into the tertiary *amine* (2·48 g., 48%), m. p. 154—162°. Recrystallisation gave needles from methanol, or prisms and thick plates from toluene, m. p. in each case 163—164° (slight decomp., with sintering from 160°) (Found: C, 73·4; H, 7·5; N, 4·5%). In a later run, the yield based on the dihydro*iso*quinoline hydrochloride was 75%.

Resolution of the Bases (IId *and* e).—The 6-ethoxy-7-methoxy-isomer (IIe) was resolved as the neutral quinate, a solution of the salt in hot acetone containing 10% of methanol rapidly depositing the salt of the (−)-base, which after a further crystallisation was decomposed, to give the pure (−)-base as prisms [from light petroleum (b. p. 100—120°)], m. p. 146° (shrinking from 120°), $[\alpha]_D^{20}$ −102° (*c* 2·24 in $CHCl_3$), unchanged by further recrystallisation of the quinate. The mother-liquors from the resolution slowly deposited the quinate of the impure (+)-base, which on liberation had $[\alpha]_D^{20}$ +77° (*c* 1·07 in $CHCl_3$), unchanged by further recrystallisation of the quinate. Neither the hydrogen tartrate nor the hydrogen malate was obtained crystalline.

The 7-ethoxy-6-methoxy-isomer (IId) was resolved as the hydrogen malate by crystallisation from acetone. In nearly every case the salt that separated (square plates or prisms) gave an inactive base, but on rare occasions the salt of the (−)-base separated as thick rhombs. Once

seeds were available, the first crop of crystals could always be obtained as the salt of the (−)-base. The mother-liquors very slowly deposited the salt of the impure (+)-base as needles. The pure bases had m. p. 130—131°, $[\alpha]_D^{17}$ +83° (*c* 0·72 in $CHCl_3$), and $[\alpha]_D^{19}$ −82° (*c* 0·66 in $CHCl_3$), decreasing *ca.* 1° per degree rise in temperature.

OO'-Diethylisochondrodendrine.—Ether (30 c.c.) containing diazoethane (0·114 g.) was added to a suspension of *iso*chondrodendrine (0·11 g.) in 1 : 1 benzene–methanol (40 c.c.), and the solution kept (several days) until all the diazoethane had decomposed. Isolation of the non-phenolic product gave 0·10 g. (80%). Addition of light petroleum (b. p. 60—80°) to a solution of this product in benzene gave the *ether* as square plates, m. p. 216°, $[\alpha]_D^{20}$ −9° (*c* 0·735 in EtOH) [Found: C, 73·5; H, 6·9; N, 4·4%; no. of *O*-alkyl groups, 4·0. $C_{34}H_{36}O_2N_2(OMe)_2(OEt)_2$ requires C, 73·8; H, 7·1; N, 4·3%]. The base was much more soluble in the common solvents than was cycleanine.

Fission of OO'-Diethylisochondrodendrine.—To a solution of sodium (*ca.* 60 mg.) in liquid ammonia (100 c.c.) a solution of *OO'*-diethyl*iso*chondrodendrine (92·6 mg.) in dry toluene (20 c.c.) was added, and the solution left for an hour. It was still blue, and the ammonia was allowed to evaporate, some undissolved sodium collected, and the residue separated into a non-phenolic portion (23·2 mg.), presumably starting material, and a crude brown phenolic resin (58·1 mg.). Extraction of the latter with ether left a small part undissolved, and the ether-soluble portion was recrystallised from light petroleum (b. p. 60—80°) to give two crops of crystals, each with m. p. 128° (51·3 mg. in all). A second crystallisation, from light petroleum (b. p. 100—120°), gave a product of m. p. 129—129·5°; a mixture with (−)-1 : 2 : 3 : 4-tetrahydro-1-4'-hydroxybenzyl-7-ethoxy-6-methoxy-2-methyl*iso*quinoline (IId) had m. p. 129—130°; a mixture with the 6-ethoxy-7-methoxy-isomer (IIe) had no definite m. p., but after softening from *ca.* 80° about half of the mixture melted suddenly at 116—117°. This second crop had $[\alpha]_D^{20\cdot5}$ −80° (*c* 0·336 in $CHCl_3$); pure (IId) had $[\alpha]_D^{20}$ −82°, and an equimolecular mixture of (IId) and (IIe) would have $[\alpha]_D^{20}$ = −92°.

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THE UNIVERSITIES OF GLASGOW AND LEEDS. [*Received, April 18th,* 1956.]

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857. *Wessely–Moser Rearrangement with Xanthones.*

By (MRS.) E. M. PHILBIN, J. SWIRSKI, and T. S. WHEELER.

1 : 4-Dihydroxy-7-methoxyxanthone (I; R = Me) when treated with hydriodic acid under pressure rearranged to form 1 : 2 : 7-trihydroxyxanthone (IV).

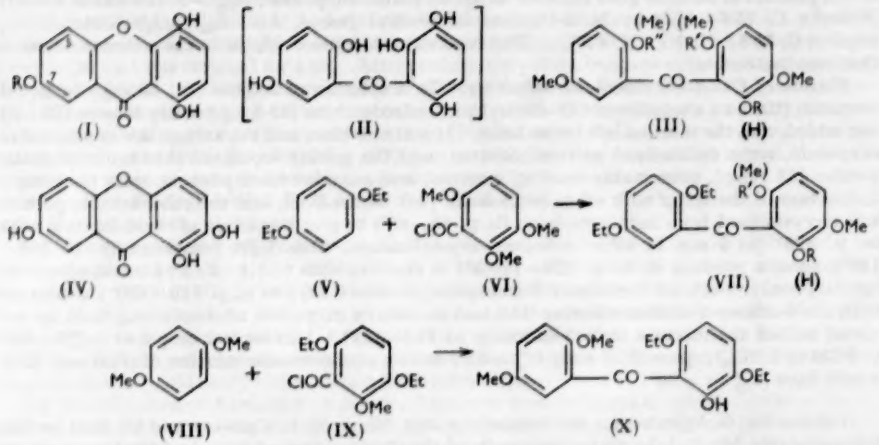
RAO AND SESHADRI [1] found that 1 : 4-dihydroxy-7-methoxyxanthone (I; R = Me) when heated with hydriodic acid did not undergo the Wessely–Moser type of rearrangement [2] (5 : 8- to 5 : 6-dihydroxyflavone), but gave the normal product, 1 : 4 : 7-trihydroxyxanthone (I; R = H). It has now been found [3] that compound (I; R = Me) when demethylated by hydriodic acid under sufficiently drastic conditions yields by rearrangement the corresponding 1 : 2 : 7-trihydroxyxanthone (IV), with, presumably, intermediate formation of the diaryl ketone (II). This is in agreement with the mechanism proposed for this type of rearrangement in flavones.[4]

The structure of the compound (IV) was confirmed by its synthesis from 2 : 3 : 6-trimethoxybenzoyl chloride (VI) and quinol dimethyl ether. Analysis showed the product to be a monohydroxytetramethoxydiphenyl ketone (III; R + R' + R'' = H + 2Me) with a hydroxyl group *ortho* to the carbonyl group (positive ethanolic ferric reaction). The compound was simultaneously demethylated and cyclised by hydriodic acid or by

[1] Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1947, **26**, *A*, 288.
[2] Wessely and Moser, *Monatsh.*, 1930, **56**, 97.
[3] Cf. Philbin, Swirski, and Wheeler, *Chem. and Ind.*, 1955, 445.
[4] Shah, Mehta, and Wheeler, *J.*, 1938, 1555.

aluminium chloride in benzene to form a trihydroxyxanthone which was not the 1 : 4 : 7-trihydroxy-compound (I; R = H) and could only be the isomer (IV). Efforts to synthesise the latter from 2-formyl-1-hydroxy-7-methoxyxanthone by application of the Dakin reaction were unsuccessful.

The position of the hydroxyl group in the ketone (III), for which there are three possibilities (R or R′ or R″ = H), was determined by the following considerations: (*a*) Condensation of 2 : 3 : 6-trimethoxybenzoyl chloride (VI) with quinol diethyl ether (V) gave a compound



with a positive ethanolic ferric reaction which analysis proved to be a 2 : 5-diethoxyphenyl hydroxydimethoxyphenyl ketone (VII; R + R′ = H + Me). This result showed that dealkylation had occurred in the acid chloride nucleus. Again: (*b*) 3 : 6-Diethoxy-2-methoxybenzoyl chloride (IX) when condensed with quinol dimethyl ether (VIII) gave an isomer of the ketone (VII) which also exhibited an ethanolic ferric reaction, and which could only have structure (X). Compound (III) is, accordingly, 2-hydroxy-3 : 6-dimethoxyphenyl 2 : 5-dimethoxyphenyl ketone (III; R = H; R′ = R″ = Me). It is clear that demethylation precedes cyclisation when this compound is converted into the trihydroxyxanthone (IV) by treatment with hydriodic acid or by aluminium chloride.

Experimental

Ethanol was employed for crystallisation if no solvent is mentioned.

Formation of 1 : 2 : 7-*Trihydroxyxanthone* (IV) *from* 1 : 4-*Dihydroxy*-7-*methoxyxanthone* (I; R = Me).—1 : 4-Dihydroxy-7-methoxyxanthone [1] (0·4 g.) was heated with hydriodic acid (10 ml.; *d* 1·7) in a sealed tube at 175—185° for 1 hr., and the product was poured into aqueous sodium hydrogen sulphite. The precipitated 1 : 2 : 7-*trihydroxyxanthone* [see (*a*) below], on repeated crystallisation, formed yellow-brown aggregates (0·1 g.), m. p. 270° (decomp.) (Found: C, 64·3; H, 3·5. $C_{13}H_8O_5$ requires C, 63·9; H, 3·3%). It exhibited a yellowish-green fluorescence in concentrated sulphuric acid and gave a dark greenish-brown colour with ethanolic ferric chloride. The *triacetate*, prepared by the acetic anhydride–sodium acetate method, formed needles, m. p. 215—217° (Found: C, 61·2; H, 3·8. $C_{19}H_{14}O_8$ requires C, 61·6; H, 3·8%). The mixed m. p. with 1 : 4 : 7-triacetoxyxanthone (m. p. 189—190°) was 160—170°.

The Ullmann condensation between quinol monomethyl ether and 2-chloro-6-methoxybenzoic acid (Ullmann and Panchaud [2]) which is involved in the preparation of 1 : 4-dihydroxy-7-methoxyxanthone proceeded more smoothly when a trace of iodine was added to the copper-bronze catalyst. If moisture was present cyclisation by sulphuric acid of the intermediate diphenyl ether gave 7-hydroxy-1-methoxyxanthone in place of the dimethoxyxanthone. This

[2] Ullmann and Panchaud, *Annalen*, 1906, **350**, 108.

result confirms the observation by Graebe and Aders [6] that treatment of 1 : 7-dimethoxyxanthone with 90% sulphuric acid produced demethylation in the 7-position. Hydriodic acid at 60° has now been found to behave similarly.

2-Formyl-1-hydroxy-7-methoxyxanthone.—1-Hydroxy-7-methoxyxanthone [1] (1 g.), hexamine (3 g.), and glacial acetic acid (10 ml.) were heated together on a boiling-water bath for 6 hr. Hot hydrochloric acid (15%; 10 ml.) was added and heating was continued for ½ hr. The mixture was diluted with an equal volume of water. The precipitated *aldehyde* separated from benzene and from ethyl acetate in yellow needles (0·4 g.), m. p. 203—204° (Found: C, 66·7; H, 3·8. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). It was insoluble in alkali and gave a reddish-brown colour with ethanolic ferric chloride. The *phenylhydrazone* formed orange plates, m. p. 198—200° (Found: C, 69·3; H, 4·4; N, 7·7. $C_{21}H_{16}O_4N_2$ requires C, 70·0; H, 4·5; N, 7·8%). Attempts to replace the formyl group by hydroxyl (Dakin reaction) by use of alkaline hydrogen peroxide at 0°, room temperature, or 100°, or of ethereal hydrogen peroxide, were unsuccessful.

1 : 2 : 7-*Trihydroxyxanthone* (IV).—(*a*) 2 : 3 : 6-Trimethoxybenzoic acid separated from water in plates, m. p. 148—150° (Found: C, 56·1; H, 5·7. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%). Gilman and Thirtle [7] give m. p. 145—146°. It was conveniently prepared from 2 : 3 : 6-trimethoxyacetophenone [8] by alkaline hypochlorite oxidation using a method previously employed by Cartwright, Jones, and Marmion [9] for the preparation of 2 : 6-dimethoxybenzoic acid. The trimethoxy-acid chloride (b. p. 139°/1·5 mm.) was prepared from the acid and thionyl chloride.

(*b*) *2-Hydroxy-3 : 6-dimethoxyphenyl 2 : 5-dimethoxyphenyl ketone* (III; R = H, R′ = R″ = Me). 2 : 3 : 6-Trimethoxybenzoyl chloride (9 ml.) was added with stirring to a mixture of aluminium chloride (15 g.), quinol dimethyl ether (5·2 g.), and ether (120 ml.) during ½ hr. After 2 days the mixture was treated with crushed ice and concentrated hydrochloric acid (25 ml.), and the product heated on a steam-bath. Benzene was added and the mixture refluxed for ½ hr. The benzene layer was extracted with 10% aqueous sodium hydroxide. Carbon dioxide precipitated from the alkaline liquid *2-hydroxy-3 : 6-dimethoxyphenyl 2 : 5-dimethoxyphenyl ketone* (2·1 g.) which crystallised in yellow needles, m. p. 115—116° (Found: C, 63·7; H, 5·6; OMe, 38·6. $C_{17}H_{18}O_6$ requires C, 64·1; H, 5·7; OMe, 39·0%). The ethanolic ferric reaction was green.

(*c*) *Demethylation of* (III; R = H, R′ = R″ = Me). (i) A mixture of the diphenyl ketone (III; R = H, R′ = R″ = Me) (1·5 g.), aluminium chloride (8 g.), and benzene (50 ml.) was refluxed on a steam-bath for 2 hr. The solvent was evaporated and the residue was treated with crushed ice and concentrated hydrochloric acid (25 ml.) and heated on a water-bath for 10 min. The resulting mixture yielded, to ether, 1 : 2 : 7-trihydroxyxanthone (IV) which crystallised from ethanol and then from ethyl acetate in yellow-brown aggregates (0·3 g.), m. p. 270° (decomp.) (triacetate, m. p. 215—217°, not depressed by addition of the triacetate of the trihydroxyxanthone obtained by demethylation and rearrangement of 1 : 4-dihydroxy-7-methoxyxanthone as described above.

(ii) A mixture of the benzophenone (1 g.) in glacial acetic acid (5 ml.) and hydriodic acid (10 ml.) was refluxed for 90 min. and poured into aqueous sodium hydrogen sulphite. The product was identical with that obtained as in (i).

Proof of the Structure of the Diphenyl Ketone (III; R = H, R′ = R″ = Me).—(*a*) 2 : 5-*Diethoxyphenyl 2-hydroxy-3 : 6-dimethoxyphenyl ketone* (VII; R = H, R′ = Me). A mixture of 2 : 3 : 6-trimethoxybenzoyl chloride (VI) (1·5 g.), quinol diethyl ether (V) (2 g.), aluminium chloride (7 g.), and ether (100 ml.) was treated as described in the preparation of (III; R = H, R′ = R″ = Me). The resulting *diphenyl ketone* formed pale yellow plates (0·15 g.), m. p. 100—101° (Found: C, 66·4; H, 6·6; OMe, 35·5. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4; 2OMe + 2OEt as 4OMe, 35·8%). It gave a green colour with ethanolic ferric chloride.

(*b*) 3 : 6-*Diethoxy-2-hydroxyphenyl 2 : 5-dimethoxyphenyl ketone* (X). A mixture of 2-methoxy-3 : 6-dihydroxyacetophenone [8] (10 g.), ethyl sulphate (30 ml.), potassium carbonate (50 g.), and acetone (200 ml.) was refluxed for 6 hr. The product was filtered and the solvent evaporated from the filtrate. The residue was dissolved in ether and the solution was washed with 5% aqueous sodium hydroxide. 3 : 6-*Diethoxy-2-methoxyacetophenone* which remained on removal of ether separated from dilute ethanol in needles (5·6 g.), m. p. 45° (Found: C, 65·9; H, 7·7; OMe, 39·7. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6; 2OEt + OMe as 3OMe, 39·1%).

[6] Graebe and Aders, *ibid.*, 1901, **318**, 367.
[7] Gilman and Thirtle, *J. Amer. Chem. Soc.*, 1944, **66**, 858.
[8] Baker, *J.*, 1939, 956.
[9] Cartwright, Jones, and Marmion, *J.*, 1952, 3499.

Oxidation of the acetophenone as described above for **2 : 3 : 6**-trimethoxybenzoic acid gave **3 : 6-*diethoxy*-2-*methoxybenzoic acid***, plates, m. p. 160—161° (Found: C, 60·1; H, 6·7; OMe, 38·6. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7; OMe + 2OEt as 3OMe, 38·7%). The acid chloride (IX) which was a solid at room temperature had b. p. 158°/2 mm. A mixture of aluminium chloride (7 g.), quinol dimethyl ether (VIII) (2 g.), and **3 : 6**-diethoxy-2-methoxybenzoyl chloride (IX) (4 g.) in ether (70 ml.) was treated as described in the preparation of (III). **3 : 6-*Diethoxy*-2-*hydroxyphenyl* 2 : 5-*dimethoxyphenyl ketone*** separated in yellow plates (0·2 g.), m. p. 102—103° (Found: C, 66·2; H, 6·3; OMe, 35·4. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4; 2OMe + 2OEt as 4OMe, 35·8%). It gave a green colour with ethanolic ferric chloride.

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858. *Acyl* iso*Thiocyanates. Part I. The Synthesis of Esters of N-Acyldithiocarbamic Acids.*

By D. T. ELMORE, J. R. OGLE, and (in part) (MRS.) W. FLETCHER and P. A. TOSELAND.

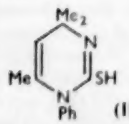
Esters of *N*-acyldithiocarbamic acids (I), which were required for the stepwise degradation of peptides from the end bearing a free amino-group,[1] have been synthesised by the interaction of acyl *iso*thiocyanates and thiols. Side-reactions, which occurred in some cases, have been elucidated.

DURING an investigation of a new method of stepwise degradation of peptides from the end bearing a free amino-group,[1] it became necessary to synthesise a number of *N*-acyldithiocarbamic esters (I). The only methods previously reported are due to Delépine [2] and Wheeler and Merriam.[3] The former method, which has been used in isolated cases only, involves the treatment of alkyl dithiocarbamates or dialkyl iminodithiocarbonate hydriodides with acid anhydrides at 100°. In the second method, thio-acids, which are of limited accessibility in spite of improved methods of synthesis recently described,[4] are caused to react with alkyl thiocyanates in refluxing benzene. A number of *N*-acyldithiocarbamic esters cannot be prepared by this route, since some thiocyanic esters are either too unstable to be isolated or would isomerise to *iso*thiocyanates under the conditions of the reaction with thio-acids.

Dixon and Doran [5] showed that acyl *iso*thiocyanates with alcohols readily give *N*-acylthioncarbamic esters (II), and it seemed probable that thiols would behave similarly to

(I) $R{\cdot}CO{\cdot}NH{\cdot}CS_2R'$

(II) $R{\cdot}CO{\cdot}NH{\cdot}CS{\cdot}OR'$



(III)

give the desired *N*-acyldithiocarbamates. Although alcohols generally react additively with acyl *iso*thiocyanates, stronger nucleophilic agents such as amines [5,6] and hydrazines [7] show a marked proclivity for substitution, with liberation of thiocyanic acid. The two

[1] Elmore and Toseland, *J.*, 1954, 4533.
[2] Delépine, *Bull. Soc. chim. France*, 1903, **29**, 48, 53.
[3] Wheeler and Merriam, *J. Amer. Chem. Soc.*, 1901, **23**, 283.
[4] Cronyn and Jiu, *ibid.*, 1952, **74**, 4726; Sheehan and Johnson, *ibid.*, p. 4726.
[5] (*a*) Dixon, *J.*, 1895, **67**, 1041; 1899, **75**, 375, 388; 1906, **89**, 892; Dixon and Doran, *J.*, 1895, **67**, 565; Doran, *J.*, 1896, **69**, 324; (*b*) 1901, **79**, 906.
[6] (*a*) Dixon, *J.*, 1889, **55**, 300, 618; 1891, **59**, 551; 1896, **69**, 855, 1593; 1897, **71**, 617; 1904, **85**, 807; Cook, Downer, and Heilbron, *J.*, 1948, 1262; Cook, Heilbron, and Smith, *J.*, 1949, 1440; (*b*) Dixon and Doran, *J.*, 1905, **87**, 331; Dixon and Hawthorne, *J.*, 1905, **87**, 468; Hawthorne, *J.*, 1906, **89**, 556; (*c*) Dixon and Taylor, *J.*, 1908, **93**, 684.
[7] Hoggarth, *J.*, 1949, 1161.

mechanisms often operate competitively and the factors which influence the course of the reaction are not yet clear, although in several cases temperature has an important effect.[6b] Further, it appears that aroyl *iso*thiocyanates react additively in the majority of cases.

In the present work, it has been observed that alkanethiols react smoothly with acyl *iso*thiocyanates to give *N*-acyldithiocarbamic esters in good yield; there was no evidence for the formation of *S*-alkyl thioesters. Acyl *iso*thiocyanates have commonly been prepared by the interaction of lead thiocyanate and acyl chlorides in dry boiling benzene. We have found it more convenient in general to use potassium thiocyanate and dry acetonitrile in which the reactants were soluble. In many cases dry acetone proved to be a satisfactory alternative solvent,[6c] although in one instance its use led to a side-reaction which is discussed below. Production of most aliphatic acyl *iso*thiocyanates was complete in 15 minutes at room temperature or in 1—2 minutes at the boiling point. Aroyl *iso*thiocyanates were formed more slowly and the reaction mixture was heated under reflux for about 15 minutes. The instability of chloroacetyl *iso*thiocyanate required reaction at 0°. It was not necessary to isolate the pure acyl *iso*thiocyanates: an excess of alkanethiol was added to the mixture containing the *iso*thiocyanate, and reaction was conducted at room temperature, usually for about 12 hours.

Reaction of acetyl chloride and potassium thiocyanate in acetone followed by addition of methanethiol afforded a minute yield of methyl *N*-acetyldithiocarbamate (I; R = R′ = Me). The bulk of the product was a foul-smelling, undistillable oil. With aniline this did not give the expected acetanilide or *N*-acetyl-*N*′-phenylthiourea but, instead, 1 : 4-dihydro-2-mercapto-4 : 4 : 6-trimethyl-1-phenylpyrimidine (III), which had previously been synthesised by Mathes, Stewart, and Swedish [8] by brief heating of mesityl oxide with ammonium thiocyanate, aniline, and hydrochloric acid. It is apparent that some of the acetone used as solvent was converted into mesityl oxide by the action of acetyl chloride during the synthesis of methyl *N*-acetyldithiocarbamate. The above oil afforded no identifiable product with *cyclo*hexylamine, an observation which is consonant with the results of Mathes *et al.*[8] It was shown that methyl *N*-acetyldithiocarbamate and *cyclo*hexylamine afforded *N*-acetyl-*N*′-*cyclo*hexylthiourea in high yield; thus the low yield of methyl *N*-acetyldithiocarbamate from acetyl chloride, potassium thiocyanate, and methanethiol in acetone was not due to inadequate isolation. Reaction in acetonitrile gave the desired product in good yield.

A further difficulty was encountered in the synthesis of phenyl *N*-benzoyldithiocarbamate (I; R = R′ = Ph). When the reaction mixture from benzoyl *iso*thiocyanate and thiophenol was poured into water benzamide was the only identifiable product. It is not clear whether this arose by the action of water on benzoyl *iso*thiocyanate [6c] or by hydrolysis of phenyl *N*-benzoyldithiocarbamate. By avoiding the use of water during the isolation, however, the desired compound was isolated, albeit in poor yield.

Synthesis of methyl and benzyl *N*-benzyloxycarbonyldithiocarbamate (I; R = $Ph{\cdot}CH_2{\cdot}O$, R′ = Me or $Ph{\cdot}CH_2$) proved extremely troublesome. A single preparation of each from benzyl chloroformate and potassium thiocyanate in acetonitrile followed by addition of either methanethiol or toluene-ω-thiol gave good yields of these compounds, but could not be reproduced. Many variations of the procedure always gave benzyl thiocyanate as the major product, and carbon dioxide was evolved. It is almost certain that these resulted from the nucleophilic attack by thiocyanate anion on either benzyl chloroformate or benzyloxycarbonyl *iso*thiocyanate, a reaction comparable with the dealkylation of esters of phosphoric acids by anions and tertiary bases.[9] It was not possible to decide between these two alternatives, but the isolation of benzyl thiocyanate in >50% yields eliminates the possibility of debenzylation of the *N*-benzyloxycarbonyldithiocarbamate esters as a major reaction. We therefore reluctantly used a less polar solvent for the formation of the acyl *iso*thiocyanate in order to keep the ionic strength of thiocyanate at a minimum. Doran [5b] reported that reaction of alkyl chloroformates and sodium thiocyanate in benzene at room temperature was extremely slow. We confirm this, since

[8] Mathes, Stewart, and Swedish, *J. Amer. Chem. Soc.*, 1948, **70**, 1452.
[9] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815; Clark and Todd, *J.*, 1950, 2023, 2030; Miyano, *J. Amer. Chem. Soc.*, 1955, **77**, 3524; Zervas and Dilaris, *ibid.*, p. 5354.

after reaction of benzyl chloroformate and excess of finely ground potassium thiocyanate in benzene at room temperature for periods of up to two weeks, addition of thiols in general gave poor yields of *N*-benzyloxycarbonyldithiocarbamates, whereas addition of excess of aniline afforded high yields of benzyl carbanilate and aniline hydrochloride. These could only have arisen from unchanged benzyl chloroformate. Reaction between benzyl chloroformate and potassium thiocyanate in toluene or benzene containing 10—20% of acetonitrile, however, proceeded at a convenient rate with no sign of concomitant debenzylation. Addition of methane- or toluene-ω-thiol to the resultant solution of benzyloxycarbonyl *iso*thiocyanate gave the desired compounds, although a week at room temperature was required to obtain optimal yields. As a final refinement, solvent was removed under reduced pressure below 40° after the first step and replaced by acetonitrile, in which the subsequent addition of thiol proceeded in at most two days.

The insolubility of *N*-acyldithiocarbamate esters in water so far used for the stepwise degradation of peptides, has required the use of aqueous ethanol or aqueous dioxan as solvent,[1] in which many peptides and proteins are rather insoluble. To provide a reagent which would be water-soluble at the pH value at which condensation with peptides occurs, synthesis of carboxymethyl *N*-acyldithiocarbamates (I; R′ = CH_2·CO_2H) was attempted. Benzoyl *iso*thiocyanate and thioglycollic acid in acetone gave a good yield of carboxymethyl *N*-benzoyldithiocarbamate (I; R = Ph, R′ = CH_2·CO_2H), but 2 : 4-dichlorobenzoyl *iso*thiocyanate gave an impure product. Attempted purification of the latter by recrystallisation afforded ethyl *N*-2 : 4-dichlorobenzoylthioncarbamate (II; R = $C_6H_3Cl_2$, R′ = Et) identical with a synthetic sample. The most probable explanation for the formation of this compound is that the reaction between 2 : 4-dichlorobenzoyl *iso*thiocyanate and thioglycollic acid was incomplete at the time of working up, and that addition subsequently occurred between the former and ethanol present in the chloroform which was employed as the solvent for recrystallisation. Prolonged reaction between 2 : 4-dichlorobenzoyl *iso*thiocyanate and thioglycollic acid at 37° afforded a small yield of carboxymethyl *N*-2 : 4-dichlorobenzoyldithiocarbamate (I; R = $C_6H_3Cl_2$, R′ = CH_2·CO_2H). Numerous attempts to synthesise carboxymethyl *N*-acetyldithiocarbamate (I; R = Me, R′ = CH_2·CO_2H) were unsuccessful. Occasionally, a high-melting, yellow, amorphous solid, probably a polymer, was obtained which could not be purified. Attempts to isolate carboxymethyl *N*-acetyldithiocarbamate as its *cyclo*hexylammonium salt failed; the only identifiable product was di(*cyclo*hexylammonium) dithiodiglycollate, identical with a synthetic sample. The yield and behaviour of this material during successive recrystallisations suggested that the oxidation of thioglycollate to dithiodiglycollate occurred during this process: a synthetic sample of *cyclo*hexylammonium thioglycollate, however, was stable during recrystallisation under the same conditions.

Although carboxymethyl *N*-acyldithiocarbamates are soluble in aqueous solution at slightly alkaline pH values, their suitability as reagents for the stepwise degradation of peptides remains to be ascertained. It has recently been shown that carboxymethyl *N*-aryldithiocarbamates are unstable at neutral pH in presence of Zn^{2+} ions,[10] and, if the mechanism postulated for this decomposition is correct, the degradation of carboxymethyl *N*-acyldithiocarbamates would probably be even more rapid. As zinc occurs in proteins such as insulin and carboxypeptidase, carboxymethyl *N*-acyldithiocarbamates may find only a limited use in stepwise degradation studies on peptides and proteins.

Experimental

For most experiments potassium thiocyanate was dried overnight at 100°/0·1 mm. over phosphoric oxide. Acetonitrile and acetone were shaken successively with calcium chloride and anhydrous calcium sulphate, distilled, and stored over anhydrous calcium sulphate.

Methyl N-Benzoyldithiocarbamate (I; R = Ph, R′ = Me).—Benzoyl chloride (14 g.) and potassium thiocyanate (9·8 g.) were allowed to react in refluxing acetonitrile (50 c.c.) for 15 min., then the mixture was cooled to 0°, treated with methanethiol (5 g.), kept overnight at room temperature with exclusion of moisture, and was poured into water (750 c.c.). The product

[10] Van der Kerk, Pluygers, and de Vries, *Rec. Trav. chim.*, 1955, **74**, 1262.

(17·5 g.) separated as a yellow solid and, after recrystallisation from ethanol, had m. p. 134° (Wheeler and Merriam [3] report m. p. 135°).

Methyl N-2 : 4-*Dichlorobenzoyldithiocarbamate* (I; R = 2 : 4-$Cl_2C_6H_3$, R′ = Me).—In a similar manner, 2 : 4-dichlorobenzoyl chloride (14 g.), potassium thiocyanate (7 g.), and methanethiol (5 g.) gave *methyl* N-2 : 4-*dichlorobenzoyldithiocarbamate* (17 g.) as pale yellow needles [from ethyl acetate–light petroleum (b. p. 40—60°)], m. p. 126—127° (Found : C, 38·8; H, 2·9; N, 5·0; S, 22·9; Cl, 25·2. $C_9H_7ONS_2Cl_2$ requires C, 38·6; H, 2·5; N, 5·0; S, 22·9; Cl, 25·3%).

Methyl N-p-*Nitrobenzoyldithiocarbamate* (I; R = *p*-$NO_2{\cdot}C_6H_4$, R′ = Me).—This *ester* (65% yield) was prepared by the foregoing method from *p*-nitrobenzoyl chloride. Recrystallised from aqueous ethanol, it had m. p. 101—104° depending on the rate of heating (Found : C, 42·4; H, 3·4; N, 10·9; S, 25·2. $C_9H_8O_3N_2S_2$ requires C, 42·2; H, 3·1; N, 10·9; S, 25·0%).

Methyl N-3 : 5-*dinitrobenzoyldithiocarbamate* [I; R = 3 : 5-$(NO_2)_2C_6H_3$, R′ = Me) was afforded in 64% yield, but was initially rather gummy. It was recrystallised three times from ethanol, then having m. p. 171—173° after softening at 163° (Found : C, 36·2; H, 2·4; N, 14·3. $C_9H_7O_5N_3S_2$ requires C, 35·9; H, 2·3; N, 14·0%).

Methyl N-*Acetyldithiocarbamate* (I; R = R′ = Me).—A mixture of acetyl chloride (7·7 g.) and potassium thiocyanate (9·7 g.) in acetonitrile (50 c.c.) was shaken for 1 hr. at room temperature, cooled to 0°, and treated with methanethiol (5 g.). The product (11·7 g.), which crystallised overnight, was isolated by pouring the mixture into water; recrystallised from chloroform–light petroleum (b. p. 40—60°), it had m. p. 117—118°. Wheeler and Merriam [3] report m. p. 119°.

Several attempts to carry out this reaction in acetone afforded only minute yields of the required compound together with a foul-smelling, undistillable, yellow oil. Addition of a solution of aniline in ethanol gave after 2 weeks at room temperature good yields of 1 : 4-dihydro-2-mercapto-4 : 4 : 6-trimethyl-1-phenylpyrimidine (III), m. p. 200—201° after recrystallisation from dioxan. Mathes *et al.*[4] report m. p. 192—193°. A sample prepared by their method had m. p. 200—201° alone or mixed with our material; the infrared spectra of the two samples were indistinguishable (Found : C, 67·1; H, 6·7; N, 11·7; S, 13·9. Calc. for $C_{13}H_{16}N_2S$: C, 67·2; H, 6·9; N, 12·1; S, 13·8%). Both specimens were converted into their S-*mercury derivatives* by mercuric oxide in ethanol under reflux, and were isolated by filtration through Hyflo-Supercel and addition of water to the filtrate; they had m. p. 183—184° alone or in admixture, and identical infrared spectra (Found : C, 46·9; H, 4·6; N, 8·3; S, 9·4. $C_{26}H_{30}N_4S_2Hg$ requires C, 47·1; H, 4·6; N, 8·4; S, 9·7%).

N-*Acetyl*-N′-cyclo*hexylthiourea*.—A solution of methyl *N*-acetyldithiocarbamate (6 g.) and *cyclo*hexylamine (5 g.) in benzene (30 c.c.) was kept for 3 weeks. Removal of solvent afforded the crystalline *urea* (5·4 g.), which after recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) and then from ethanol, had m. p. 104—105° (Found : C, 54·0; H, 8·5; N, 14·1; S, 16·2. $C_9H_{16}ON_2S$ requires C, 54·0; H, 8·1; N, 14·0; S, 16·0%).

Methyl N-*Propionyldithiocarbamate* (I; R = Et, R′ = Me).—This *compound* (80%) was prepared by allowing propionyl chloride and potassium thiocyanate to react at room temperature in acetonitrile. After the mixture had stood with methanethiol overnight, potassium chloride was removed and the filtrate was evaporated under reduced pressure. The product, crystallised from ethanol, had m. p. 106—108° (Found : C, 36·5; H, 5·7; N, 8·9. $C_5H_9ONS_2$ requires C, 36·8; H, 5·6; N, 8·6%).

Methyl N-*Dichloroacetyldithiocarbamate* (I; R = $CHCl_2$, R′ = Me).—The method described for the *N*-propionyl derivative afforded this *dithiocarbamate* (71%) as a brown solid, m. p. 123° (from moist ethanol) (Found : C, 22·1; H, 2·1; N, 6·1; Cl, 33·0. $C_4H_5ONS_2Cl_2$ requires C, 22·0; H, 2·3; N, 6·4; Cl, 32·5%).

Methyl N-*Chloroacetyldithiocarbamate* (I; R = CH_2Cl, R′ = Me).—At room temperature chloroacetyl chloride and potassium thiocyanate reacted vigorously and gave tars. Consequently, the acyl chloride (11·3 g.) in acetonitrile (50 c.c.) was shaken at 0° and powdered potassium thiocyanate (9·7 g.) was added portionwise during 90 min. After a further 30 min., methanethiol (5 g.) was added and the mixture was allowed to warm to room temperature and left overnight. The *product* (11·9 g.), isolated in the usual way, recrystallised from ethanol as light yellow plates, m. p. 114—115° with effervescence. It decomposed rapidly in hot aqueous ethanol and soon became coloured in air (Found : C, 25·9; H, 3·5; S, 34·4. $C_4H_6ONS_2Cl$ requires C, 26·2; H, 3·3; S, 34·9%).

Phenyl N-*Benzoyldithiocarbamate* (I; R = R′ = Ph).—Addition of thiophenol to benzoyl *iso*thiocyanate in acetonitrile proceeded slowly and the mixture was kept 11 days at room temperature under nitrogen. The solution was filtered and evaporated under reduced pressure

to an oil which was extracted with benzene. Addition of light petroleum (b. p. 40—60°) caused a yellow oil to separate, which partially crystallised at 0°. Three recrystallisations of the solid fraction from carbon tetrachloride gave *phenyl* N-*benzoyldithiocarbamate* (7%), m. p. 98—99° (Found: C, 61·2; H, 4·2; N, 5·6; S, 23·2. $C_{14}H_{11}ONS_2$ requires C, 61·5; H, 4·1; N, 5·1; S, 23·5%). Attempts to isolate the dithiocarbamate by pouring the reaction mixture into water gave benzamide as the only crystalline product.

Methyl N-*Benzyloxycarbonyldithiocarbamate* (I; R = Ph·CH_2O, R′ = Me).—For the following reactions, which were conducted in heterogeneous media, potassium thiocyanate was obtained in a finely divided state by pouring an ice-cold, saturated, ethanolic solution with stirring into 4 volumes of ether at 0°.

(*a*) Benzyl chloroformate (8·5 g.), potassium thiocyanate (24·5 g.), and some glass beads were shaken in a mixture of toluene (400 c.c.) and acetonitrile (100 c.c.) at room temperature for 2 days. Potassium salts were removed and washed with toluene, and the combined filtrates were allowed to react with methanethiol (5 g.) at room temperature for a week. The solution was concentrated under reduced pressure, then kept at 0°; the *product* (8·1 g.), when collected and recrystallised from aqueous ethanol, had m. p. 133·5—134·5°. A further quantity (1·3 g.) was obtained from the mother-liquors by concentration and addition of light petroleum (b. p. 40—60°) (Found: C, 50·2; H, 4·6; N, 5·9. $C_{10}H_{11}O_2NS_2$ requires C, 49·8; H, 4·6; N, 5·8%).

(*b*) A solution of benzyloxycarbonyl *iso*thiocyanate, prepared as above in benzene (400 c.c.) and acetonitrile (100 c.c.), was concentrated under reduced pressure below 40° and with a nitrogen leak, to approximately 100 c.c. Acetonitrile (100 c.c.) and methanethiol (5 g.) were added and the solution was kept at room temperature during 2 days. The product (6·2 g.), isolated as described above and recrystallised, had m. p. 133·5—134·5°.

When pure acetonitrile was used as solvent, the major product as a rule was benzyl thiocyanate, whilst in pure benzene reaction between benzyl chloroformate and potassium thiocyanate (10 molar excess) was so slow that after 2 weeks addition of aniline to the filtered reaction mixture afforded high yields of benzyl carbanilate and aniline hydrochloride (cf. Doran [55]).

Benzyl N-*Benzyloxycarbonyldithiocarbamate* (I; R = Ph·CH_2O, R′ = Ph·CH_2).—This *compound* (50—70%) was prepared by the two methods given for the methyl ester, except that only 1 molar quantity of toluene-ω-thiol was employed. It was almost colourless after recrystallisation from aqueous ethanol and had m. p. 113—114° (Found: C, 60·4; H, 4·7; N, 4·8. $C_{16}H_{15}O_2NS_2$ requires C, 60·5; H, 4·8; N, 4·4%).

Carboxymethyl N-*Benzoyldithiocarbamate* (I; R = Ph, R′ = CH_2·CO_2H).—Equivalent quantities of benzoyl *iso*thiocyanate and thioglycollic acid were kept in acetone solution for 36 hr. at room temperature. Pouring the mixture into water gave the *ester* (60%) as an oil which rapidly crystallised. Recrystallised from ethyl acetate, it had m. p. 156° after softening at 130° and varying with the rate of heating (Found: C, 47·3; H, 3·6; N, 5·3. $C_{10}H_9O_2NS_2$ requires C, 47·0; H, 3·6; N, 5·5%).

Carboxymethyl N-2 : 4-*Dichlorobenzoyldithiocarbamate* (I; R = 2 : 4-$Cl_2C_6H_3$, R′ = CH_2·CO_2H).—A mixture of 2 : 4-dichlorobenzoyl *iso*thiocyanate and thioglycollic acid in acetonitrile was kept at 38° during 10 days. The oily *dithiocarbamate*, which separated in water, solidified at 0° (m. p. 149—155°). After two recrystallisations from chloroform–ethanol (9 : 1) and one from ethanol, it had m. p. 162—163° after darkening above 155° (Found: C, 37·5; H, 2·6; N, 4·3; S, 19·2; Cl, 21·2. $C_{10}H_7O_3NS_2Cl_2$ requires C, 37·0; H, 2·2; N, 4·3; S, 19·8; Cl, 21·9%). In an earlier attempt to synthesise this compound, the reactants were kept in acetone at room temperature during 12 hr. The gummy solid, which separated when the mixture was poured into water, was repeatedly recrystallised from chloroform–light petroleum (b. p. 40—60°). It proved to be *ethyl* N-2 : 4-*dichlorobenzoylthiocarbamate* (II; R = 2 : 4-$Cl_2C_6H_3$, R′ = Et), m. p. 99—100°, undepressed on admixture with an authentic sample. The two samples had identical infrared spectra (Found: C, 42·8; H, 3·5; N, 4·7; S, 11·4; Cl, 25·5. $C_{10}H_9O_2NSCl_2$ requires C, 43·2; H, 3·3; N, 5·0; S, 11·5; Cl, 25·5%).

Ethyl N-2 : 4-*Dichlorobenzoylthiocarbamate*.—A solution of 2 : 4-dichlorobenzoyl *iso*thiocyanate (0·025 mole) in acetonitrile (50 c.c.) and ethanol (5 c.c.) was kept at room temperature during 48 hr. and was then poured into water. The resulting yellow oil (6 g.) solidified at 0° and was recrystallised from aqueous ethanol (charcoal) and then from chloroform–light petroleum (b. p. 40—60°); the *ester* had m. p. 99—100° (Found: C, 43·2; H, 3·5; N, 5·1%).

Attempted Addition of Thioglycollic Acid to Acetyl iso*Thiocyanate*.—Numerous attempts to bring about this reaction failed to give a crystalline product. On two occasions, a yellow, amorphous solid was formed which did not melt below 310°. From its physical properties it

appeared to be a polymer, but no consistent analyses could be obtained. An attempt to isolate the required dithiocarbamate as its *cyclo*hexylammonium salt gave only *di*(cyclo*hexylammonium*) *dithiodiglycollate*. After several recrystallisations from ethanol–ether, this had m. p. 169—170°, undepressed on admixture with an authentic sample and having an identical infrared spectrum (Found: C, 50·2; H, 8·2; N, 6·8; S, 16·4. $C_{16}H_{32}O_4N_2S_2$ requires C, 50·5; H, 8·5; N, 7·4; S, 16·8%).

The authentic sample was obtained in quantitative yield from dithiodiglycollic acid and *cyclo*hexylamine in ethanol (m. p. 169·0—169·5°) (Found: C, 50·3; H, 8·4; N, 7·0; S, 16·6%).

cyclo*Hexylammonium Thioglycollate*.—This *salt*, obtained in quantitative yield from *cyclo*hexylamine and thioglycollic acid in benzene, had m. p. 119—120° after recrystallisation from ethanol–ether (Found: C, 50·0; H, 8·8; N, 7·2. $C_8H_{17}O_2NS$ requires C, 50·2; H, 9·0; N, 7·3%).

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859. *The Electrical Conductances of Solutions in Nitric Acid. Part I. Solutions of Dinitrogen Pentoxide, and of Water. The Extent of the Self-dissociation of Nitric Acid.*

By W. H. Lee and D. J. Millen.

The electrical conductivities of anhydrous nitric acid, and of solutions of dinitrogen pentoxide, and of water, in nitric acid, have been measured, at −10° and at −20°. On the basis of the self-dissociation, $2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$, the extent of this dissociation has been found. The product of the mole fractions of NO_2^+, NO_3^-, and H_2O, *i.e.*, the classical mole fraction dissociation constant K_x, is found to be $0{\cdot}930 \times 10^{-4}$ at −10°, and $1{\cdot}602 \times 10^{-4}$ at −20°, the molar concentrations of each species being 0·511 and 0·610 at the respective temperatures.

Several studies of the self-dissociation of nitric acid have yielded a consistent picture of the ionic and molecular species formed. The extent of the process has been estimated from cryoscopic studies by Dunning and Nutt [1] and by Gillespie,[2] both of which apply at the freezing point, −42°.

In the present work, the same self-dissociation process is assumed, *viz.*,

$$2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O \quad . \quad . \quad . \quad . \quad . \quad (A)$$

and the extent of dissociation is calculated from the change in the electrical conductivity when dinitrogen pentoxide and water are dissolved in nitric acid. Both of these solutes are solvent self-dissociation products, so that a study of their solutions is particularly relevant, and indeed necessary before the conductivities of other solutes in nitric acid can be interpreted.

A number of conductivity studies on solutions in nitric acid have been reported. Veley and Manley [3] measured the conductivities of solutions of water in nitric acid. They observed a conductivity minimum at approximately 2 molal water, which was confirmed by Dalmon [4] and by the present work, though Hantzsch had been unable to find it. Berl and Saenger [5] studied solutions of dinitrogen pentoxide in nitric acid, at 18°. They

[1] Dunning and Nutt, *Trans. Faraday Soc.*, 1951, **47**, 15.
[2] Gillespie, *J.*, 1950, 2552.
[3] Veley and Manley, *Phil. Trans.*, 1898, **191**, 365.
[4] Dalmon, *Mem. Services chim. État*, 1943, **30**, 141.
[5] Berl and Saenger, *Monatsh.*, 1929, **54**, 1036.

reported a maximum conductivity at high solute concentrations, but, as these solutions were yellow, some decomposition must have occurred. Taylor, Lyne, and Follows [6] studied nitric acid solutions of dinitrogen pentoxide, water, and ammonium nitrate, at several temperatures. These previous results show the same general trend as those of the present investigation, but the higher temperatures employed increased the possibility of serious errors due to solvent decomposition.

Very few conclusions were drawn from previous studies, and no attempt was made to deduce the extent of solvent self-dissociation.

Experimental

Measurements were taken at $-10°$ and $-20°$ to avoid, as far as possible, thermal decomposition of nitric acid or dinitrogen pentoxide. The temperature was maintained by a glycol–alcohol bath, cooled by a commercial refrigerator unit, and controlled by a toluene–mercury regulator and subsidiary heaters to within $\pm 0{\cdot}02°$. Resistance was measured by a conventional Wheatstone bridge circuit, supplied by an oscillator with switched frequency control. To obviate catalytic decomposition of the solvent by platinum black, the electrodes were of bright platinum; measurement at different frequencies showed that no appreciable errors due to polarisation were introduced.

Since the solvent and the solutions had very high specific conductances a capillary-tube conductivity cell, of Pyrex glass, having a high cell-constant, was used. The electrodes were about 0·5 cm. square, separated by 20 cm. of capillary tubing. The cell was calibrated at 0° by means of 0·1D-potassium chloride described * by Jones and Bradshaw.[7] The cell constant so obtained was 232·4 at 0°, and this value was also used for measurements made at $-10°$ and $-20°$, since no calibrating solutions are available for use at these temperatures. It was estimated that contraction of the cell and electrodes could lead to a change in cell constant of about 0·05% at the lower temperature, and this is beyond the accuracy with which the composition of the solutions is known.

Densities of solutions were measured by means of a syphon pyknometer, designed for use with anhydrous liquids (Hennion [8]). It was calibrated with absolute ethanol, at $-10°$, and had a volume of 2·656 ml.

Preparation of Reagents.—Nitric acid was prepared by static distillation, from a mixture of fuming nitric acid and sulphuric acid, as described by Reed.[9] The product was redistilled in a smaller apparatus, reserved for this purpose. The composition of the product is discussed below.

Dinitrogen pentoxide was prepared by distillation, in a current of ozonised oxygen, from a nitric acid–phosphoric oxide mixture at room temperature. The product was passed through phosphoric oxide drying-tubes before condensation in a trap cooled in alcohol–carbon dioxide.

Good quality, laboratory-distilled water, of specific conductance below 10^{-6} ohm^{-1}, was used.

Solutions were prepared by weight. Dinitrogen pentoxide was re-distilled, through drying-tubes, into a known weight of nitric acid. Water was added from a weight pipette to a known weight of the well-cooled acid. To avoid contamination of solutions during several transfers, the densities were determined on separately prepared solutions.

Results

The specific conductances of the solutions are recorded in Table 1, and densities in Table 2.

* Parker and Parker (*J. Amer. Chem. Soc.*, 1924, **46**, 312) originally defined a demal solution as being one containing 1 mole of solute per cubic decimeter of solution, in air at 0°. For potassium chloride solutions Jones and Bradshaw [7] recommend standard solutions, based on measurements of electrical conductivity of mercury and the international ohm, as follows: D, 71·1352; 0·1D, 7·41913; 0·01D, 0·745263 g. of KCl per 1000 g. of solution *in vacuo*. See Robinson and Stokes, "Electrolyte Solutions," Butterworths, London, 1955, Chap. 5.

[6] Taylor, Lyne, and Follows, *Canad. J. Chem.*, 1951, **29**, 439.
[7] Jones and Bradshaw, *J. Amer. Chem. Soc.*, 1933, **55**, 1780.
[8] Hennion, *Ind. Eng. Chem.*, 1937, **9**, 479.
[9] Reed, *J.*, 1950, 2438.

TABLE 1. *Specific conductances of solutions in nitric acid.*

(Concns. are in molarities, and specific conductances in ohm^{-1}.)

$T = -10{\cdot}02°$.

$[N_2O_5]$	$10^4\kappa$	$[N_2O_5]$	$10^4\kappa$	$[N_2O_5]$	$10^4\kappa$	$[N_2O_5]$	$10^4\kappa$
0·085	385	0·3082	441	0·4288	477	0·7061	570
0·1018	390	0·3893	455	0·5033	498	1·279	725
0·2109	413	0·4130	468	0·5502	505	1·880	817
$[H_2O]$	$10^4\kappa$	$[H_2O]$	$10^4\kappa$	$[H_2O]$	$10^4\kappa$	$[H_2O]$	$10^4\kappa$
0·0498	358	0·2886	309	0·3383	297	0·5916	260
0·1503	335	0·3121	301	0·5096	272	1·175	188
0·2225	321						

$T = -20{\cdot}01°$.

$[N_2O_5]$	$10^4\kappa$	$[H_2O]$	$10^4\kappa$	$[H_2O]$	$10^4\kappa$	$[H_2O]$	$10^4\kappa$
0·1505	366	0·1202	321	0·2266	308	0·3908	283
0·4544	438	0·1788	310	0·2890	295		

TABLE 2. *Densities of solutions in nitric acid.*

$T = -10{\cdot}02°$.				$T = -20{\cdot}01°$.			
$[N_2O_5]$	$d_{soln.}$	$[H_2O]$	$d_{soln.}$	$[N_2O_5]$	$d_{soln.}$	$[H_2O]$	$d_{soln.}$
0·0976	1·5652	0·3988	1·5614	0·1490	1·582	0·1205	1·580
0·1991	1·5663	0·4993	1·5610	0·4498	1·584	0·1792	1·578
0·4001	1·5694	—	—	—	—	0·2897	1·578
0·5981	1·5736	0·7215	1·5590	—	—	0·3917	1·577
0·7262	1·5757	1·9719	1·5544				
1·7297	1·6116						

For the solvent, as prepared by static distillation, the mean values for 20 samples gave the results :

Specific conductance	0·0348 ± 0·0003 ohm^{-1} at −10°
Density	1·5630 ± 0·0002 g. ml.$^{-1}$,,

If the conductivities of solutions of both water and dinitrogen pentoxide are plotted against composition of solution, a smooth curve is obtained, giving no indication of the position of " nitric acid." Addition of dinitrogen pentoxide to nitric acid increases the conductivity; addition of water to nitric acid decreases it. Both solutes, however, produce a freezing-point depression, so that the freezing point–composition graph passes through a maximum at the composition of nitric acid. The properties of the pure acid may thus be unequivocally determined on the liquid of maximum freezing point.

A combined study of the cryoscopy and conductivity of nitric acid has recently been made by Gillespie and Lewis.[10] They find the product of the static distillation to contain 0·10 mole of " excess " water, per litre of nitric acid. The acid of maximum freezing point (−41·64°) has a specific conductance 0·0367 ohm^{-1} at −10°. From our density–composition graph, this acid has a density 1·5644 g. ml.$^{-1}$ at −10°. These values for the pure solvent have been adopted in the interpretation of our results. The concentrations recorded in Tables 1 and 2 have been calculated on this basis.

Calculation of the Extent of Self-dissociation.—Evidence for the dissociation of nitric acid according to equation (*A*) has been summarised by Gillespie and Millen.[11] Cryoscopic evidence shows that dinitrogen pentoxide is completely ionised in nitric acid, but that water is practically un-ionised;[2] and on this basis, the conductivity results in Table 1 may be qualitatively explained.

The increase in conductivity on dissolving dinitrogen pentoxide in nitric acid is a measure of the increased concentration of nitronium and nitrate ions, only partially offset by the repression of solvent self-dissociation. With water as solute, no extra ions are

[10] T. J. Lewis, Ph.D. Thesis, London, 1954.
[11] Gillespie and Millen, *Quart. Rev.*, 1948, **2**, 282.

added, and the decrease in conductivity is due solely to the repression of self-dissociation. Beyond the broad conductivity minimum, at approximately 2m-water, the hydroxonium ion appears in significant concentration, and, together with the reduced viscosity, this accounts for the increase in conductivity with further addition of water.

The Conductance-Concentration Relation applicable to Solutions in Nitric Acid.—To develop these ideas quantitatively, a relation between conductance and concentration is needed. Preliminary study showed that the dilute-solution law, $\Lambda \propto \sqrt{c}$, was of little value, except that its failure indicated a much higher degree of self-ionisation than is found for other solvents.

It is observed that, for aqueous solutions of a single electrolyte, within the concentration range 0·3—1·0m, the equivalent conductance varies only slowly with concentration; this variation is about 5% (over the range considered) for alkali halides, and about 7% for the nitrates. Thus, within this range, it is a better approximation to take Λ constant, and therefore $\kappa \propto c$, the molarity, rather than $\Lambda \propto \sqrt{c}$. This is equivalent to assuming that there is no change in the ionic mobilities, and that the change in κ is entirely due to the change in the number of ions per unit volume, over this range. The molar concentration of ions in the nitric acid solvent will be shown to be about 0·5; so that, by comparison with aqueous solutions, the relation $\kappa \propto c$ might be expected to apply here, particularly if the dielectric constant of nitric acid is not very different from that of water. There is evidence that this is so, from conductivity measurements of solutions of salts, not containing the nitrate ion, in nitric acid,[12] and from direct measurement by the moving ellipsoid method.[13] We adopt this relation, which, although only approximate, enables all the conductivity results to be combined in finding an accurate value for the extent of the self-dissociation.

Application of the Relationship $\kappa \propto c$ to Conductivities of Solutions in Nitric Acid.—Suppose the molar concentration of each ion, and of water, in anhydrous nitric acid, to be a; then one litre of nitric acid contains $(1000d/M - 2a)$ mole of the species "HNO_3," where d is the density of the acid, and M its molecular weight. The term $(1000d/M)$ has the value 24·825 at −10°, and 25·103 at −20°.

Suppose further that, after the addition of m moles of dinitrogen pentoxide to one litre of nitric acid, there are present n g.-ions of nitrate and nitronium ions. Then we may deduce the amounts of the other species present in the solution, and also the volume of the solution; for convenience, these amounts, together with those present in the pure solvent, are given in Table 3.

TABLE 3. *Number of moles of species present, at −10°.*

System	HNO_3	NO_2^+	NO_3^-	H_2O	Volume of system
Anhydrous nitric acid	$24{\cdot}825 - 2a$	a	a	a	1 litre
1 litre of nitric acid, with m mole of N_2O_5 added	$24{\cdot}825 - 2n$	n	n	$n - m$	$1/D$ litre

The density of the solvent is denoted by d, that of the solution by $d_{soln.}$ and D is $1000d_{soln.}/(1000d + 108m)$. Expressions for K_x, the self-dissociation equilibrium constant, with concentrations expressed in mole fractions are :

$$\text{for the solvent,} \qquad K_x = \frac{a^3}{(24{\cdot}825 + a)(24{\cdot}825 - 2a)^2} \cdot f_1^2 \cdot \frac{f_2}{f_3^2} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and, for the solution :

$$K_x = \frac{n^2(n - m)}{(24{\cdot}825 + n - m)(24{\cdot}825 - 2n)^2} \cdot \frac{f'_1{}^2 f'_2}{f'_3{}^2} \quad . \quad . \quad . \quad . \quad (2)$$

where f_1 is the mean ion activity coefficient of $NO_2^+NO_3^-$, f_2 the activity coefficient of water, and f_3 that of nitric acid, all in the pure solvent; and f'_1, f'_2, f'_3 are the corresponding values

[12] W. H. Lee, Ph.D. Thesis, London, 1953.
[13] R. F. M. White, personal communication.

for the solution. Similar considerations for solutions of water lead to an analogous equation :

$$K_s = \frac{n^2(n+m)}{(24{\cdot}825+n-m)(24{\cdot}825-2n)^2} \cdot \frac{f''_1{}^2 f''}{f''_3{}^2} \quad . \quad . \quad . \quad . \quad (3)$$

in which n has the same significance as before, but m is now the number of moles of water added to one litre of nitric acid.

Applying the relationship $\kappa \propto c$ previously considered, to the solvent and solution of Table 3, we obtain :

$$\kappa_{\text{soln.}}/\kappa_{\text{HNO}_3} = nD/a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Substituting for a^3, in eqn. (1), and combining it with eqn. (2), we have :

$$(\kappa_{\text{soln.}}/\kappa_{\text{HNO}_3})^3 = \frac{n^3D^3(24{\cdot}825+n-m)(24{\cdot}825-2n)^2}{n^2(n-m)(24{\cdot}825-2a)^2(24{\cdot}825+a)} \cdot \frac{f_1{}^3 f_2 f'_3{}^2}{f_3{}^3 f'_1{}^2 f'_2} \quad . \quad . \quad (5)$$

Neglecting the activity coefficient product, we may solve for n, giving :

$$n = m/[1 - D^3(\kappa_{\text{HNO}_3}/\kappa_{\text{soln.}})^3 \cdot \beta] \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where $\beta = (24{\cdot}825+n-m)(24{\cdot}825-2n)^2/(24{\cdot}825-2a)^2(24{\cdot}825+a)$

Similarly, for solutions of water, n may be evaluated from the equation :

$$n = m/[\beta' D^3(\kappa_{\text{HNO}_3}/\kappa_{\text{soln.}})^3 - 1] \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $\beta' = (24{\cdot}825+n+m)(24{\cdot}825-2n)^2/(24{\cdot}825-2a)^2(24{\cdot}825+a)$

Now β and β' are both functions of a and n, but, since they are only slowly varying functions and do not depart appreciably from unity, equations (6) and (7) may be readily solved by a method of successive approximations; n is effectively constant after three such approximations.

From each value of n, a value of a may be obtained, from $a = nD \cdot \kappa_{\text{HNO}_3}/\kappa_{\text{soln.}}$. Any dependence of the calculated value of a upon n will indicate departure from the assumptions made concerning the conductance–concentration relation and the neglect of activity coefficients. Variation of a with n is in fact found; but its effect can be overcome by extrapolation to find the value of a as m approaches zero. The form of equation 6 is such that the values of a become less reliable as m decreases. However, since extrapolation is possible for solutions of both water and dinitrogen pentoxide, the procedure reduces to an interpolation of the value of a for that mixture in the N_2O_5–H_2O system corresponding to the composition HNO_3.

The results obtained at $-20°$ may be treated in the same way, by using density factors appropriate to this temperature, the term 24·825 being replaced by 25·103.

The results of these calculations, for solutions of dinitrogen pentoxide and of water at $-10°$, together with the experimental results, are recorded in Table 4, and those at $-20°$ in Table 5.

TABLE 4.

$T = -10{\cdot}02°$. $10^4\kappa_{\text{HNO}_3} = 368$ ohm^{-1}. $d = 1{\cdot}564$ g. ml.$^{-1}$.

Molarity of N_2O_5	$10^4\kappa_{\text{soln.}}$	$d_{\text{soln.}}$	n	a	Molarity of H_2O	$10^4\kappa_{\text{soln.}}$	$d_{\text{soln.}}$	n	a
0·1024	390	1·565	0·558	0·523	0·0498	358	1·564	0·573	0·588
0·2057	415	1·566	0·600	0·525	0·1500	335	1·563	0·456	0·499
0·3101	441	1·568	0·661	0·541	0·2002	325	1·562	0·438	0·494
0·4156	468	1·569	0·730	0·560	0·2504	315	1·562	0·416	0·484
0·5224	500	1·571	0·854	0·609	0·3005	305	1·562	0·394	0·472
0·6304	535	1·574	0·868	0·576	0·3505	295	1·561	0·367	0·455
0·7400	574	1·576	0·936	0·575	0·4104	288	1·561	0·364	0·462
					0·5023	273	1·561	0·341	0·456

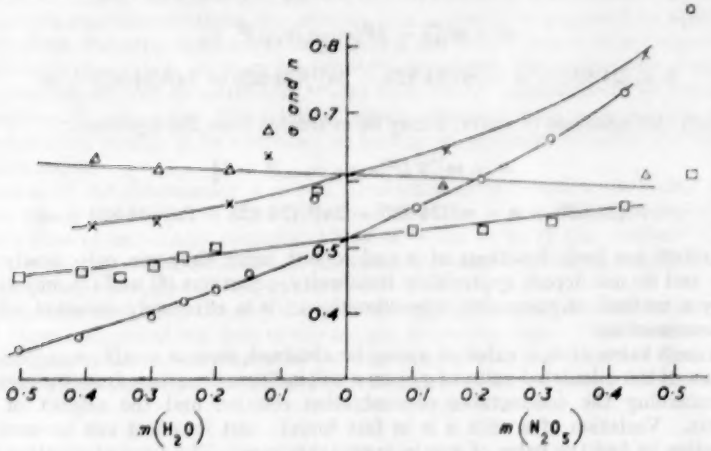
TABLE 5.

$T = -20{\cdot}01°$. $10^4\kappa_{HNO_3} = 340$ ohm^{-1}. $d = 1{\cdot}582$ g. ml.$^{-1}$.

Molarity of N_2O_5	$10^4\kappa_{calc.}$	$d_{calc.}$	n	a	Molarity of H_2O	$10^4\kappa_{calc.}$	$d_{calc.}$	n	a
0·1505	366	1·582	0·645	0·593	0·1202	321	1·580	0·637	0·672
0·4544	438	1·584	0·790	0·605	0·1788	310	1·578	0·562	0·613
					0·2890	295	1·578	0·538	0·614
					0·3908	283	1·577	0·528	0·630

The Figure shows a plot of the calculated values of a against m. It is seen, that although there is a slight dependence of the value for a on m, there is no difficulty in obtaining the interpolated value of a at $m = 0$. Also shown in the same diagram is a plot of the calculated values of n against m. It will be seen that the curves intersect satisfactorily at $m = 0$. This intersection is very dependent on the value used for the specific

Graphical interpolation to obtain values for a, the molarity of water, nitrate, and nitronium ions in anhydrous nitric acid. All concentrations are expressed in molarities. ○, *n at* −10·02°. ×, *n at* −20·01°. □, *a at* −10·02°. △, *a at* −20·01°.



conductance of the solvent and affords a sensitive test for the correctness of the value taken.

Table 6 records the values of a obtained for the two temperatures, the mole fractions of nitronium ion $x_{NO_2^+}$ ($= x_{NO_3^-} = x_{H_2O}$), and also the values of the classical mole fraction dissociation constants.

TABLE 6.

	a	$x_{NO_2^+}$	$x_{HNO_3^-}$	10^5K_x
At −10·02°	0·511	0·0194	0·942	0·930
At −20·01°	0·606	0·0227	0·932	1·602

TABLE 7. *The classical self-dissociation constant for nitric acid at various temperatures.*

Temp.	10^5K_x	Ref.
−40°	2·44	1, 10
−20	1·602	Present work
−10	0·930	,,
+25	0·280	6

By similar calculations from the conductance data of Taylor *et al.*[6], K_x has been found at 25°. These values are summarised in Table 7, together with a value for a temperature of −40° obtained cryoscopically.

The variation of K_s may account in part for the temperature-dependence of the specific conductance of nitric acid, which shows a maximum at about 25°; this result [6] has been confirmed in the present investigation. Thus, despite a continuous decrease in viscosity, the specific conductance falls above 25°, because there is an even greater effect due to the decrease in the number of ions present. Other factors which may contribute are changes in solvation of the ions and variation in the dielectric constant, with temperature, and it is hoped to investigate these later.

The equivalent conductance of nitronium nitrate, given by $\Lambda = l_{NO_2^+} + l_{NO_3^-} = 1000\kappa/c$, is found to have the values, 55·7 at −20°, 71·9 at −10°, and 107·4 at 25°, for the solutions corresponding to anhydrous nitric acid. The corresponding values for the pure solvents, water and sulphuric acid, at 25° are 536 and 166·3. The low value obtained for the ions produced by the self-ionisation of nitric acid may be due in part to the high concentration of ions in this case. However, the main cause of the higher values for water and sulphuric acid is probably the chain-conductance mechanism which operates in both of these cases; [14] as will be shown later, no such mechanism has been observed in nitric acid.

The award of an F.E. and T. grant by the Ministry of Education to one of us (W. H. L.) is gratefully acknowledged. We are indebted to Drs. R. J. Gillespie and T. J. Lewis for information, before publication, about the properties of nitric acid of maximum freezing point.

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William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, April 20th*, 1956.]

[14] Gillespie and Wasif, *J.*, 1953, 970.

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860. *The Chemistry of Extractives from Hardwoods. Part XXVII.* The Structure of Terminolic Acid.*

By F. E. King and T. J. King.

Terminolic acid, $C_{30}H_{48}O_6$, a tetrahydroxy-triterpene of the oleanolic acid series, has been conclusively related to arjunolic acid [2 : 3 : 23(or 24)-trihydroxyolean-12-en-28-oic acid] through the formation of methyl arjunolate on forced Wolff–Kishner reduction of methyl terminonate, a monoketonic oxidation product of methyl terminolate.

The position of the hydroxyl group thus eliminated was inferred from the acid-catalysed dehydration of methyl terminonate to a cyclic enol ether, a reaction attributed to the condensation of the carbonyl and the 23(or 24)-hydroxyl group. From further data which indicate a relationship to sumaresinolic acid it is concluded that the fourth hydroxyl group occupies the 6-position and has the β(axial)-conformation.

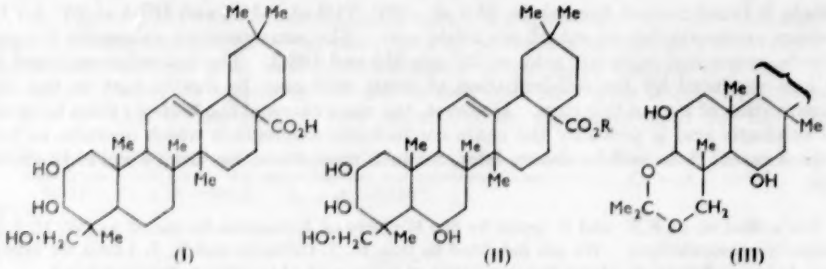
Terminolic acid,[1] $C_{30}H_{48}O_6$, is a new triterpene isolated from *Terminalia ivorensis* during an examination of the heartwood of certain *Terminalia* species. It belongs to the oleanolic acid series and resembles arjunolic acid, which was recently obtained from *T. arjuna* and identified as 2 : 3 : 23(or 24)-trihydroxyolean-12-en-28-oic acid [2] (I). Terminolic acid is a tetrahydroxy-compound, and its botanical association with arjunolic acid led us tentatively to regard it as a hydroxyarjunolic acid. Further investigation has confirmed this and it has now been shown that the triterpene from *T. ivorensis* is 6β-hydroxyarjunolic acid (II; R = H).

Immediately after the experiments recorded in Part XXIII,[1] it was observed that methyl terminolate (II; R = Me) yielded a highly crystalline *iso*propylidene compound. This new derivative—actually (III; R = Me)—in contrast to the parent ester, was

* Part XXVI, *J.*, 1956, 1384.

[1] King, King, and Ross, *J.*, 1955, 1333.
[2] *Idem*, *J.*, 1954, 3995.

resistant to periodate oxidation, and its formation therefore involved at least one of the hydroxyl groups in the original 1 : 2-glycol. With acetic anhydride–pyridine the methyl *O-iso*propylideneterminolate yielded an acetate, which although at first believed to be a diacetyl compound, was shown on further consideration of the acetylation products of the triterpene to be a monoacetate. Mild hydrolysis of the acetate eliminated the *iso*propylidene residue leaving an acetoxy-triol which, like methyl *O-iso*propylideneterminolate, was unaffected by sodium periodate. It was thus apparent that the *iso*propylidene compound



(III; R = Me) is the derivative of a 1 : 3-glycol, such as, for example, the 3 : 23-diol hederagenin, and the probable occurrence in terminolic acid of a 3 : 23(or 24)-glycol unit was substantiated by the isolation of formaldehyde from the copper-catalysed pyrolysis of methyl terminolate.[3] The evidence of the periodate test implies, moreover, that the acetylisable substituent of the *iso*propylideneterminolate must be located at the 2-position. Consequently, terminolic acid contains the 2 : 3 : 23(or 24)-trihydroxy-system present in arjunolic acid (I).

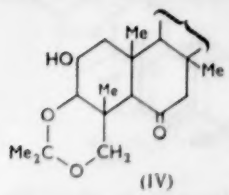
Oxidation of methyl *O-iso*propylideneterminolate revealed a marked difference between the remaining hydroxyl groups. When the chromic oxide–pyridine reagent [4] was used, the product consisted of a mono-oxo-compound [methyl *O-iso*propylideneterminonate (IV; R = Me)], and attempts to prepare a diketone led to degradation, presumably in the double-bond region of the molecule. Optimum yields of the keto-ester were obtained with two equivalents of oxidising agent, the second molecule apparently forming a stable chromate. The identity of the acetyl derivative of methyl *O-iso*propylideneterminonate with the product obtained by oxidation of methyl *O*-acetyl-*O-iso*propylideneterminolate indicated that the oxidised substituent was not the readily acetylated hydroxyl group.

Cautious hydrolysis of the *iso*propylideneterminonate with very dilute sulphuric acid afforded a trihydroxyketo-ester, methyl terminonate. The keto-triol was also obtained in small yield by the action of chromic oxide–pyridine on methyl terminolate, oxidation of the 3- and the 23(or 24)-hydroxyl group presumably being inhibited by the formation of a cyclic chromate. The product underwent periodate oxidation indicative of the α-glycol unit and yielded formaldehyde under the appropriate conditions of pyrolysis. No ketonic derivatives were obtainable from methyl terminonate, but this is attributable to steric hindrance of the oxo-group, the presence of which was established, however, by light absorption. Moreover, the normal Wolff–Kishner reaction was without effect on the keto-ester, but reduction of the keto-group took place under forcing conditions,[5] and the formation thereby of methyl arjunolate confirmed the intimate relationship existing between the two triterpenes.

Of the various positions available for the fourth hydroxyl group, several can be rejected forthwith—position 1, for example, being excluded by the periodate titration data which indicate the presence in terminolic acid of only one α-glycol unit. The situation of the remaining hydroxylic substituent was unexpectedly disclosed through the use of somewhat more concentrated acid (actually hydrochloric acid) for the hydrolysis of methyl *O-iso*propylideneterminonate. In place of the methyl terminonate previously formed, a product

[3] Tsuda and Kitagawa, *Ber.*, 1938, **71**, 1604.
[4] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[5] Barton, Ives, and Thomas, *J.*, 1955, 2056.

was obtained which, though tending to solvate and therefore being difficult to analyse, clearly contained less than the six oxygen atoms of the original triterpene molecule. Analysis of the crystalline diacetate and dibenzoate demonstrated conclusively the loss of a molecule of water, and this was accompanied by the disappearance of carbonyl absorption from the ultraviolet spectrum. The α-glycol system, however, remained intact and it was therefore inferred that the carbonyl group formed by oxidising the unorientated substituent had undergone condensation with the 23(or 24)-hydroxyl. In agreement with this conclusion methyl terminonate reacted easily and irreversibly with the more concentrated mineral acid, to form the identical anhydro-derivative. The facility with which this intra-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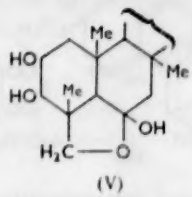
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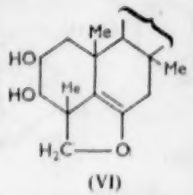
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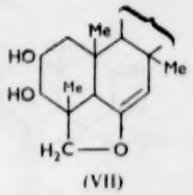

(VII)

molecular condensation occurs thus restricts, for stereochemical reasons, the remaining oxygenated substituent to the neighbouring 6- or 7-position.

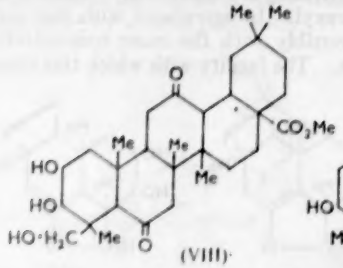
The acid-induced interaction of the carbonyl and the hydroxyl group and the accompanying loss of water were consequently attributed to hemiacetal formation followed by dehydration to an enol ether. On the assumption, later confirmed, that the carbonyl group is attached to the 6-position, the resulting products contain an additional 5-membered ring, as shown in (V; R = Me) and in (VI or VII; R = Me). Support for the enol ether formulation was found in the ultraviolet spectrum of the end product, which not only lacked the ketonic-carbonyl absorption, but also exhibited intensified absorption at 200—220 mμ due to the introduction of a new ethylenic link. This was still more evident in the case of the enol ether from methyl dihydro-12-oxoterminonate (VIII), which was prepared from methyl tri-*O*-acetyldihydro-12-oxoterminolate (described in Part XXIII as the tetra-acetate) by oxidation and hydrolysis. Acid-treatment of the product (VIII), which is devoid of ethylenic unsaturation, gave a derivative analogous to the oxide (VI or VII), having typical double-bond absorption at 200—220 mμ.

On the other hand, the absorption band at *ca.* 1660 cm.$^{-1}$ characteristic of the simple enol ethers [6] is missing from the infrared spectrum of methyl anhydroterminonate, but no comparative data are available for enol ethers which are part of a rigid, highly substituted, cyclic structure. It is possible, therefore, that in these circumstances the normal vinyl ether band is displaced towards longer wavelengths where it is obscured by the intense absorption of the methoxycarbonyl group. In view of the mild conditions required to effect the change (N/50-acid at room temperature) it is highly improbable that a skeletal change has occurred which has resulted in the migration of the double bond away from the 5 : 6-position. That drastic rearrangement has not taken place is indicated, for example, by the formation, from methyl di-*O*-acetylanhydroterminonate with one equivalent of *N*-bromosuccinimide, of a compound which has the characteristic absorption of a homoannular diene and is thus almost certainly the corresponding 9(11)-dehydro-compound.

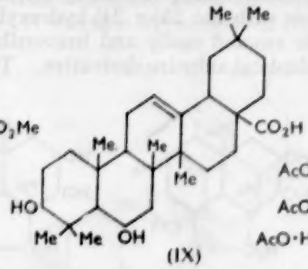
The choice of position 6 for the fourth and readily oxidisable hydroxyl group of terminolic acid rests on analogies between its derivatives and those of sumaresinolic acid [7] (IX). Methyl sumaresinonate, for example, does not give ketonic derivatives and cannot be reduced by the Wolff–Kishner method except under forcing conditions. However, the 6-hydroxyl group in sumaresinolic acid is unaffected by acetic anhydride–pyridine, and this supposed divergence in the behaviour of the respective triterpene esters led to a re-examination of the acetylation of methyl terminolate. It was then found that the product formed

[6] Meakins, personal communication; cf. *J.*, 1953, 4170.
[7] Ruzicka, Jeger, Grob, and Hösli, *Helv. Chim. Acta*, 1943, **26**, 2283; Ruzicka, Norymberski, and Jeger, *ibid.*, 1945, **28**, 380; Djerassi, Thomas, and Jeger, *ibid.*, 1955, **38**, 1304.

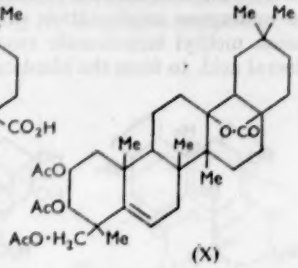
by pyridine–acetic anhydride was a triacetate and that full esterification to the tetra-acetyl compound required perchloric acid as catalyst. The position of the free hydroxyl group in methyl tri-*O*-acetylterminolate was determined by oxidation with chromic oxide–pyridine, the product being hydrolysed to methyl terminonate. Contrariwise, methyl tetra-*O*-acetylterminolate resists complete hydrolysis, a monoacetate being obtained, and in this



(VIII)



(IX)



(X)

respect also there is a resemblance to methyl sumaresinolate diacetate in which the 6-acetoxy-group is stable to alkali.

Reduction of methyl *O-iso*propylideneterminonate with sodium borohydride regenerated the original *iso*propylidene-triterpene ester, whereas sodium–ethanol reduction yielded an amorphous product. It is probable, therefore, owing to the hindered nature of the keto-group that the hydroxyl substituent in question has the β(axial)-configuration, thus further resembling the corresponding group in sumaresinolic acid.

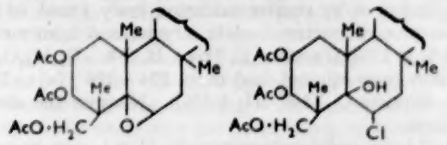
Other evidence pointing to the existence of a 6β-hydroxyl group in terminolic acid was obtained from treatment of the acid or its methyl ester with hydrobromic–acetic acid, the product after deacetylation giving a compound which appeared to be an anhydro-lactone $C_{30}H_{46}O_5$. Its composition was confirmed by the formation of a triacetate and tribenzoate, and the periodate reaction showed that the α-glycol unit remained unimpaired. An *iso*-propylidene derivative was obtained which readily formed a monoacetate. It followed therefore that the hydroxyl group eliminated was that situated in ring B, and its extrusion accompanying the formation of an unsaturated lactone (X) exactly corresponds to the behaviour of the 6β-substituent in sumaresinolic acid under similar conditions.

The resulting 5 : 6-double bond is characteristically inert, being resistant to catalytic hydrogenation and having no colour reaction with tetranitromethane. However, its presence was demonstrated by ultraviolet absorption indicative of a trisubstituted ethylenic link, and by the formation from the anhydroterminolic lactone triacetate (X) of an epoxide (XI). The nature of this product was determined by analysis, the absence of light absorption at *ca.* 290 mμ excluding the alternative keto-structure. Treatment of the acetyl-epoxide with hydrogen chloride in chloroform gave rise to a chlorohydrin formulated as (XII) by analogy with the corresponding product from the steroid 5 : 6α-epoxides.[8] Pyridine regenerated the epoxide from the chlorohydrin, whereas aqueous alkalis converted it into a trihydroxy-epoxide which was stable to hydrogen chloride in chloroform but with methanolic hydrochloric acid formed a new product believed to be a 5 : 6-diol. The chlorohydrin triacetate is unaffected by chromic oxide in both pyridine and acetic acid, thus showing the hydroxyl group to be attached to the tertiary 5-carbon atom. This supports the conclusion based on light-absorption data that anhydroterminolic lactone contains a trisubstituted double bond. The position of the unsaturated link as α to a CH_2 group was further demonstrated by oxidation of the lactone triacetate with chromic oxide–acetic acid to a derivative shown by analysis and ultraviolet absorption to be an αβ-unsaturated ketone (XIII). Oxidation has, therefore, occurred presumably at the 7-position, thus adding confirmation to the view that the hydroxyl in ring B is attached to $C_{(3)}$.

Because of the strongly acid medium used in the conversion of terminolic acid into the anhydro-lactone, the possibility of a molecular rearrangement cannot be excluded without

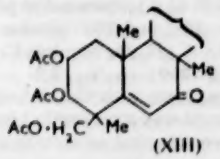
[8] Spring and Swain, *J.*, 1939, 1356.

further investigation. By reaction with hydrogen chloride–acetic acid at room temperature, methyl sumaresinolate forms an anhydro-derivative,[7] and under these milder conditions methyl terminolate also gave the anhydroterminolate (XIV), the light absorption of which was compatible with the presence of two non-conjugated double bonds. The product (XIV) was characterised by a crystalline *iso*propylidene derivative, alternatively prepared from methyl *O*-acetyl-*O*-*iso*propylideneterminolate by dehydration with phosphoryl chloride–pyridine followed by hydrolysis with aqueous alkali. Since the occurrence of carbonium ion rearrangements is highly improbable in basic media, the formation of the identical product by both methods virtually excludes the possibility of nuclear rearrangement in the preparation of the anhydroterminolate.

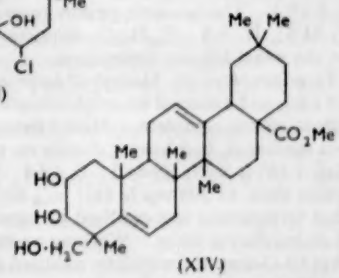


(XI)

(XII)



(XIII)



(XIV)

Finally, when oxidised with hydrogen peroxide in acetic acid, methyl tri-*O*-acetylanhydroterminolate gave an amorphous product, presumably methyl 2 : 3 : 23(or 24)-tri-*O*-acetyl-5 : 6-epoxyanhydrodihydro-12-oxoterminolate, from which was prepared a crystalline chlorohydrin. The hydroxyl group in this derivative being resistant to oxidation, the preceding epoxide must have originated in an isolated tri- or tetra-substituted double bond, *i.e.*, at the 5 : 6-position, a conclusion which provides additional support for the structure attributed to terminolic acid.

Experimental

Except where otherwise stated, acylations were in pyridine and were carried out for 12—15 hr. at room temperature or for 1 hr. at 100°, and hydrolyses with alkali were under reflux with 2N-methanolic potassium hydroxide for 1 hr. Optical rotations are recorded for chloroform solutions and sodium light at room temperature. Analytical samples were normally dried to constant weight at 150° in a vacuum or at 10° below the m. p. whichever was the lower. Light absorption data are for ethanol solutions.

Methyl O-iso*Propylideneterminolate*.—Methyl terminolate (5 g.) was treated in acetone (50 c.c.) with 3 drops of concentrated hydrochloric acid. After a few minutes the *isopropylidene derivative* began to separate in nearly cubic prisms, and after several hours at 0° the virtually pure product (5·5 g.) was collected. The crystals contained acetone of crystallisation and would not crystallise except from that solvent; they had m. p. 144—148° (effervescence), $[\alpha]$ +27° (*c* 1·22) (Found, in an air-dried specimen: C, 71·6; H, 9·5. $C_{34}H_{54}O_6,C_3H_6O$ requires C, 72·0; H, 9·8. Found, in a specimen dried at 120°: C, 73·4; H, 9·7. $C_{34}H_{54}O_6$ requires C, 73·1; H, 9·7%). The *monoacetate hydrate* crystallised from methanol in thick transparent plates which at 100° changed to a white anhydrous powder, m. p. 219—220°, $[\alpha]$ −5·5° (*c* 1·26) (Found: C, 71·6; H, 9·5. $C_{36}H_{56}O_7$ requires C, 72·0; H, 9·4%). The benzoate was amorphous.

Methyl 2-O-*Acetylterminolate*.—The above acetate (1 g.) was warmed for a few minutes in methanol containing 2 drops of concentrated hydrochloric acid. After 1 hr. the crystalline product (0·8 g.) was collected and crystallised from methanol as the hydrate as shining rectangular plates which at 100° became opaque (but retained their shape), giving the anhydrous *ester*, m. p. 220—221°, $[\alpha]$ +12° (*c* 1·24) (Found: C, 70·5; H, 9·3. $C_{33}H_{52}O_7$ requires C, 70·7; H, 9·35%). This compound was unaffected by treatment for 24 hr. at room temperature with aqueous-ethanolic sodium metaperiodate.

Methyl O-iso*Propylideneterminonate*.—Methyl *O-iso*propylideneterminolate (4 g.) in pyridine (30 c.c.) was added to pyridine–chromic oxide (30 c.c. containing 1·4 g., *ca.* 2 mol., of chromic oxide) at room temperature; the orange chromic complex immediately dissolved and was rapidly replaced by a dark brown precipitate; oxidation was complete in 1 hr. The solution was filtered, the brown solid washed with pyridine, and the combined solutions were poured into water (300 c.c.). The product was collected into ether which was washed several times with water to remove pyridine, and the solvent evaporated. A hot methanolic solution of the residue was diluted until crystallisation began, giving *methyl* O-iso*propylideneterminonate* (3·1 g.) in stout needles. Crystallised from methanol it had m. p. 232—234°, [α] +32° (*c* 0·59) (Found: C, 73·0; H, 9·2. $C_{34}H_{52}O_6$ requires C, 73·3; H, 9·4%); light absorption max. at 292 mμ (ε 30). Using the calculated amount of oxidising agent gave a 32% yield of pure product. The *acetate*, prepared by acetylation of the above alcohol or by similar oxidation (only 1 mol. of oxidising agent required) of methyl *O*-acetyl-*O-iso*propylideneterminolate, crystallised from methanol in stout needles, m. p. 239—240°, [α] +4·5° (*c* 1·05) (Found: C, 72·1; H, 8·9. $C_{36}H_{54}O_7$ requires C, 72·2; H, 9·1%). The *benzoate*, prisms from ethanol, had m. p. 274—275°, [α] −7° (*c* 0·55) (Found: C, 74·5; H, 8·3. $C_{41}H_{56}O_7$ requires C, 74·5; H, 8·5%). None of the above compounds gave the usual ketonic derivatives.

Methyl Terminonate.—(*a*) Methyl *O-iso*propylideneterminonate (1 g.) was suspended in methanol (25 c.c.), and 1 drop of 6N-sulphuric acid was added. Next day the solution was diluted until crystallisation was complete. *Methyl terminonate* (0·65 g.) separated as plates, crystallising from aqueous methanol, and having double m. p. 221—224° and 260° (double m. p. not always observed), [α] +49° (*c* 2·59) (Found: C, 72·4; H, 9·3. $C_{31}H_{48}O_6$ requires C, 72·1; H, 9·4%); light absorption max. at 293 mμ (ε 24); ε_{310} 4000; ε_{220} 1250; $\varepsilon_{310}/\varepsilon_{293}$ 3·2.

(*b*) Methyl terminolate was oxidised at room temperature with the chromic oxide–pyridine reagent (4·5 mols.) during 24 hr. Working up in the usual way gave methyl terminonate (29%).

(*c*) Methyl tri-*O*-acetylterminolate, oxidised as above, afforded an acetate which gave methyl terminonate (76%) on hydrolysis.

Methyl terminonate acetate was amorphous and no ketone derivatives could be obtained. In aqueous-ethanolic solution the ester reacted with 1·02 mols. of sodium metaperiodate, giving an amorphous neutral product.

Pyrolyses with Copper.—(*a*) A mixture of methyl terminolate (0·5 g.) and precipitated copper (3 g.) was heated at 270—290° for 1 hr., and the evolved gases were passed into saturated aqueous dimedone. After 1 hr. the precipitate (25 mg.) was collected. After it had been purified from methanol it had m. p. 188—189° alone or mixed with formaldehyde dimedone derivative.

(*b*) A similar experiment with methyl terminonate gave 30 mg. of formaldehyde dimedone derivative.

(*c*) A control experiment with methyl oleanolate gave no formaldehyde.

Reduction of Methyl Terminonate.—(*a*) Normal Wolff–Kishner reduction of methyl terminonate with anhydrous hydrazine and sodium ethoxide in ethanol at 180° gave a mixture of acids which after esterification (diazomethane) afforded a small yield of unchanged methyl terminonate together with much amorphous material, possibly methyl 6α-terminolate (see below).

(*b*) Vigorous Wolff–Kishner reduction of methyl terminonate (0·5 g.) by the process described by Barton [5] afforded, after re-esterification, methyl arjunolate (0·3 g.), m. p. and mixed m. p. 214—216°, further characterised as the triacetyl 18α-lactone, m. p. and mixed m. p. 265—266°, [α] +11° (*c* 1·4) (Found: C, 70·1; H, 8·8. Calc. for $C_{36}H_{54}O_8$: C, 70·3; H, 8·9%).

Reduction of Methyl O-iso*Propylideneterminonate*.—(*a*) Methyl *O-iso*propylideneterminonate (0·5 g.) in methanol (10 c.c.) was treated overnight with a slight excess of sodium borohydride. The excess of reagent was decomposed by acid, the solution was poured into water, and the product collected with ether. The residue, after evaporation of the solvent, was dissolved in acetone (5 c.c.) containing 1 drop of concentrated hydrochloric acid. Methyl *O-iso*propylideneterminolate (340 mg.) soon separated and was further characterised as the acetate.

(*b*) Methyl *O-iso*propylideneterminonate was reduced in the usual way with excess of sodium in boiling ethanol. The product resisted attempts to crystallise it, nor could crystalline products be obtained after removal of the *iso*propylidene group by acid hydrolysis.

Acid-rearrangement of Methyl Terminonate.—Methyl *O-iso*propylideneterminonate (2 g.), suspended in methanol (25 c.c.), was treated with 1 drop of concentrated hydrochloric acid. The solid rapidly passed into solution and after about 15 min. *methyl anhydroterminonate* began to separate. After a further 1 hr. at room temperature the product (1·4 g.) was collected; it separated from methanol or aqueous methanol in needles, m. p. 145—147° (slow heating), [α] +85° (*c* 1·0) [Found (average of 6 analyses), after drying at 110°: C, 74·4; H, 9·3. $C_{31}H_{46}O_5$

requires C, 74·7; H, 9·3%]; light absorption: ε_{210} 6000; ε_{220} 3200; $\varepsilon_{210}/\varepsilon_{220}$ 1·86; no selective absorption at *ca.* 290 mμ. The same product was obtained in almost quantitative yield on similar treatment of methyl terminonate. This ester or its *iso*propylidene derivative also afforded the anhydro-derivative after 24 hr. when dissolved in methanol containing 5 times the concentration of sulphuric acid used in the preparation of methyl terminonate from its *iso*-propylidene derivative (see above). Methyl anhydroterminonate was stable to alkali, being recovered unchanged after 6 hr. in boiling 2N-methanolic potassium hydroxide. It reacted rapidly at room temperature in aqueous ethanol with 0·97 mol. of sodium metaperiodate. The *diacetate* crystallised from methanol in thick hexagonal plates, m. p. 166—167°, [α] +20° (*c* 1·67) (Found: C, 72·0; H, 8·6; OMe, 5·4; OAc, 14·7. $C_{33}H_{50}O_7$ requires C, 72·1; H, 8·65; 1 OMe, 5·3; 2 OAc, 14·4%). Hydrolysis regenerated the diol. The *dibenzoate* crystallised from methanol in needles, m. p. 235—236° [α] −5·5° (*c* 2·5) (Found: C, 76·4; H, 8·0. $C_{45}H_{54}O_7$ requires C, 76·5; H, 7·7%).

Methyl Tri-O-acetyldihydro-12-oxoterminonate.—*Methyl tri-O-acetyldihydro-12-oxoterminolate* (1 g.) (Found: C, 67·5; H, 8·6. $C_{37}H_{56}O_{10}$ requires C, 67·25; H, 8·5%), previously described as the tetra-acetate, was oxidised with excess of chromic oxide–pyridine overnight at 0°. Working up in the usual way gave *methyl triacetyldihydro-12-oxoterminonate* (0·8 g.) in rhombic tablets (from methanol), m. p. 205°, [α] −45° (*c* 1·08) (Found: C, 67·3; H, 8·3. $C_{37}H_{54}O_{10}$ requires C, 67·45; H, 8·3%).

Methyl Dihydro-12-oxoterminonate.—Saponification of the corresponding triacetate gave *methyl dihydro-12-oxoterminonate*, flattened needles (from aqueous methanol), m. p. 208—210°, [α] −45° (*c* 1·06) (Found: C, 70·3; H, 9·0. $C_{31}H_{48}O_7$ requires C, 69·9; H, 9·1%); the compound showed no ethylenic absorption at 210—230 mμ.

Methyl Anhydrodihydro-12-oxoterminonate.—The above diketone (0·85 g.) in methanol (10 c.c.) was treated with 1 drop of concentrated hydrochloric acid. After 3 hr. water was added to the solution and *methyl anhydrodihydro-12-oxoterminonate* (0·64 g.) was precipitated; it crystallised from aqueous methanol in leaflets or prisms, m. p. 266—267°, [α] −19° (*c* 0·95) (Found: C, 72·3; H, 8·8. $C_{31}H_{46}O_6$ requires C, 72·3; H, 9·0%); light absorption: ε_{210} 2000; ε_{220} 1200. The compound was unchanged after 8 hours' boiling with 2N-methanolic potassium hydroxide. The *diacetate* crystallised in needles, m. p. 170—172°, [α] −59° (*c* 1·03), from aqueous methanol (Found: C, 69·8; H, 8·3. $C_{35}H_{50}O_8$ requires C, 70·2; H, 8·4%).

Methyl Di-O-acetylanhydrodehydroterminonate.—Methyl di-*O*-acetylanhydroterminonate (0·6 g.) with *N*-bromosuccinimide (0·18 g., 1 mol.) in carbon tetrachloride (50 c.c.) was boiled for 5 hr. The precipitated succinimide was removed and the filtrate evaporated. The residue of crude *methyl di-O-acetylanhydrodehydroterminonate* crystallised from methanol or aqueous methanol in hydrated needles (0·23 g.), m. p. 240—242°, [α] −44° (*c* 0·24) (Found, in an air-dried sample: C, 69·9; H, 8·2. $C_{35}H_{48}O_7,H_2O$ requires C, 70·2; H, 8·4. Found, in a vacuum-dried sample: C, 72·4; H, 8·3. $C_{35}H_{48}O_7$ requires C, 72·4; H, 8·3%); light absorption max. at 283 mμ (ε 7300).

Acetylation of Methyl Terminolate.—(*a*) Acetylation of methyl terminolate with acetic anhydride–pyridine gave *methyl tri-O-acetylterminolate*, crystallising from aqueous methanol or methanol in leaflets, m. p. 160—162°, [α] +19° (*c* 1·53) (Found, after drying at the m. p.: C, 69·2; H, 8·8. $C_{37}H_{56}O_9$ requires C, 68·9; H, 8·75%). Oxidation of the triacetate with chromic oxide–pyridine followed by alkaline hydrolysis gave the known methyl terminonate in excellent yield.

(*b*) Acetylation of methyl terminolate or its triacetate with acetic anhydride containing 1 drop of perchloric acid for ½ hr. at room temperature gave the tetra-acetate previously described;[1] it crystallised from methanol in tablets, m. p. 168—170°, and from aqueous methanol in rods, m. p. 187—189°, [α] −13° (*c* 1·8) (Found: C, 68·2; H, 8·6. Calc. for $C_{39}H_{58}O_{10}$: C, 68·2; H, 8·5%).

Methyl 6-O-Acetylterminolate.—Methyl tetra-*O*-acetylterminolate was hydrolysed with boiling aqueous-methanolic potassium hydroxide during 1 hr. Dilution of the solution with water precipitated the *monoacetate* which separated from aqueous methanol in flattened needles, m. p. 216—218°, [α] +21° (*c* 1·06) (Found: C, 70·5; H, 9·3. $C_{33}H_{52}O_7$ requires C, 70·7; H, 9·35%).

Anhydroterminolic Lactone.—Methyl terminolate or sodium terminolate (5 g.) was dissolved in 50% hydrogen bromide–acetic acid (50 c.c.) and after 48 hr. at room temperature the purplish-red solution was poured into water. The precipitated solid would not crystallise, so it was immediately hydrolysed for 2 hr. by boiling 2N-methanolic potassium hydroxide (150 c.c.). Cautious addition of water then precipitated a dark oil from which the solution was decanted; excess of water then precipitated the product as a yellow powder which was collected and dried. This crude product, crystallised first from slightly aqueous acetone and then from acetone, gave

the *lactone* in needles (1·4 g.), m. p. 320° (vac.), [α] +17·5° (*c* 0·8) (Found: C, 73·6; H, 9·3. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%); light absorption: ε_{210} 1300; ε_{230} 350; $\varepsilon_{210}/\varepsilon_{230}$ 3·7 (cf. for cholesterol:[9] ε_{210} 1600; ε_{230} 400; $\varepsilon_{210}/\varepsilon_{234}$ 4·0). The double bond present in anhydroterminolic lactone was inert towards catalytic reduction and failed to give a colour with tetranitromethane. In aqueous ethanol at room temperature it reacted in 2 hr. with 1·01 mol. of sodium metaperiodate. The *triacetate* crystallised from methanol in leaflets, m. p. 211—212°, [α] +8° (*c* 2·77) (Found: C, 70·2; H, 8·4. $C_{36}H_{52}O_8$ requires C, 70·55; H, 8·55%). The *tribenzoate* crystallised from ethanol in small prisms, double m. p. 262—263° and 278°, [α] +71° (*c* 1·02) (Found: C, 77·0; H, 7·25. $C_{51}H_{52}O_8$ requires C, 76·7; H, 7·3%).

Anhydro-O-isopropylideneterminolic Lactone.—Anhydroterminolic lactone (1 g.), suspended in acetone (50 c.c.), was treated with 1 drop of concentrated hydrochloric acid. The solid dissolved almost immediately and within a few minutes the *isopropylidene lactone* (1·0 g.) crystallised. It separated from ethanol in plates, m. p. 326—328° (vac.), [α] +23° (*c* 1·18) (Found: C, 74·8; H, 9·4. $C_{33}H_{50}O_5$ requires C, 75·2; H, 9·6%). The free hydroxy-group in this compound was not oxidised by chromic oxide–pyridine. The *acetate* crystallised in large prisms (from methanol), m. p. 271—272°, [α] −4° (*c* 1·8) (Found: C, 73·8; H, 9·3. $C_{35}H_{52}O_6$ requires C, 73·9; H, 9·2%). The *benzoate* crystallised from ethanol in prisms, m. p. 326—328° (vac.), [α] +10° (*c* 1·05) (Found: C, 76·5; H, 8·6. $C_{40}H_{54}O_6$ requires C, 76·15; H, 8·6%).

2-O-Acetylanhydroterminolic Lactone.—*O*-Acetylisopropylideneterminolic lactone (0·5 g.), suspended in methanol (20 c.c.), was warmed with 5 drops of concentrated hydrochloric acid during ½ hr. Water precipitated the acetyl-lactone (0·34 g.) which crystallised from methanol in flattened needles, m. p. 294°, [α] −13° (*c* 1·4) (Found: C, 73·0; H, 8·8. $C_{32}H_{48}O_6$ requires C, 72·7; H, 9·15%). The acetate did not react with periodate.

Anhydroepoxyterminolic Lactone.—Tri-*O*-acetylanhydroterminolic lactone (1·5 g.) in glacial acetic acid (15 c.c.) was treated for 3 hr. at 100° with excess (1 c.c.) of 30% hydrogen peroxide. The product was isolated by dilution with water, followed by crystallisation from aqueous methanol, giving the *acetyl-epoxide* (1·3 g.) as plates or leaflets, m. p. 244—245° after sintering at 231°, [α] −13° (*c* 1·22) (Found: C, 68·5; H, 8·4. $C_{30}H_{58}O_9$ requires C, 68·8; H, 8·3%); a solution in ethanol was virtually transparent to light of wavelength >210 mμ. Alkaline hydrolysis afforded *anhydroepoxyterminolic lactone*, crystallising from methanol in needles, m. p. 327—329° (vac.), [α] −12° (*c* 1·02) (Found: C, 71·4; H, 9·4. $C_{30}H_{46}O_6$ requires C, 71·7; H, 9·2%).

Tri-O-acetyl-6-chloro-5-hydroxyarjunolic Lactone.—Tri-*O*-acetylanhydroepoxyterminolic lactone (0·5 g.) in dry chloroform (25 c.c.) was treated at room temperature with hydrogen chloride for 1 hr. The solvent was removed in a vacuum and the residue crystallised from ethanol, giving the *chlorohydrin* (0·42 g.) as rhombic tablets, m. p. 236° (effervescence), [α] −39° (*c* 0·62) (Found: C, 64·9; H, 7·9; Cl, 5·3. $C_{36}H_{53}O_9Cl$ requires C, 65·0; H, 8·0; Cl, 5·3%). The chlorohydrin reverted to the epoxide on melting, with evolution of hydrogen chloride, or in warm pyridine. Methanolic alkali converted it into the trihydroxy-epoxide, characterised as the acetate. The chlorohydrin was recovered unchanged after treatment at room temperature with an excess of chromic oxide in acetic acid containing a little sulphuric acid, or with chromic oxide–pyridine, for 10 days.

5 : 6-Dihydroxyarjunolic Lactone.—Anhydroepoxyterminolic lactone was recovered unchanged after treatment with chloroformic hydrogen chloride for 12 hr. The lactone (0·25 g.) was then boiled for 6 hr. in methanol (25 c.c.) containing concentrated hydrochloric acid (0·5 c.c.); working up in the usual way gave the *diol*, crystallising from aqueous acetone in silky needles, m. p. 316—320° (vac.) (Found: C, 69·1; H, 9·5. $C_{30}H_{48}O_7$ requires C, 69·2; H, 9·3%).

Tri-O-acetylanhydro-7-oxoterminolic Lactone.—Tri-*O*-acetylterminolic lactone (0·9 g.) was treated with excess of chromic oxide (0·3 g.) in acetic acid (50 c.c.) containing sulphuric acid (1·0 c.c.) for 2 days at room temperature. The *product* was isolated, by pouring the solution into water, as a colourless powder which crystallised from aqueous acetone or aqueous methanol in leaflets (0·34 g.), double m. p. 194—196° and 224°, [α] −26° (*c* 0·72) (Found: C, 68·7; H, 8·25. $C_{36}H_{50}O_9$ requires C, 69·0; H, 8·0%); light absorption max. at 233 mμ (ε 11,000).

Methyl Anhydroterminolate.—Methyl terminolate (2 g.) in acetic acid (25 c.c.) was saturated with hydrogen chloride at room temperature, and after 2 days the solution was poured into water. The amorphous product was hydrolysed and the triol isolated with water and crystallised from acetone–hexane as felted needles (0·67 g.), m. p. 140° (slow heating), [α] +18° (*c* 1·5) (Found: C, 74·5; H, 9·9. $C_{31}H_{48}O_5$ requires C, 74·4; H, 9·7%); light absorption: ε_{210} 5000; ε_{230} 1500.

[9] Bladon, Henbest, and Wood, *J.*, 1952, 2737.

The acetate was amorphous. A solution of the ester in acetone with a drop of concentrated hydrochloric acid did not deposit any solid but the *isopropylidene* derivative was obtained by pouring the solution into dilute ammonia. From methanol it formed prisms and from aqueous methanol plates, m. p. 202°, [α] +47° (*c* 1·2) (Found: C, 75·2; H, 9·9. $C_{34}H_{52}O_8$ requires C, 75·5; H, 9·7%).

Methyl 2-O-*Acetylanhydro*-O-iso*propylideneterminolate*.—A solution of methyl 2-*O*-acetyl-*O*-*iso*propylideneterminolate (4 g.) in pyridine (50 c.c.) containing excess (0·5 c.c.) of phosphorus oxychloride was boiled for 3 hr. and poured into water. The precipitated solid readily crystallised from aqueous methanol as the *hydrate* (3·1 g.), m. p. 139° (slow heating), [α] +15° (*c* 0·46) (Found, in an air-dried sample: C, 71·9; H, 9·1. $C_{36}H_{54}O_9,H_2O$ requires C, 72·0; H, 9·4%), losing the solvent at the m. p. to give the anhydrous *ester* (Found: C, 74·0; H, 9·5. $C_{36}H_{54}O_8$ requires C, 74·2; H, 9·3%). Alkaline hydrolysis afforded methyl anhydro-*O*-*iso*propylideneterminolate.

Methyl 2-O-*Acetylanhydroterminolate*.—To a suspension of methyl 2-*O*-acetylanhydro-*O*-*iso*propylideneterminolate (1 g.) in methanol were added 5 drops of concentrated hydrochloric acid; the solid dissolved during ½ hr. Next day the solution was poured into water, and the dried precipitate crystallised from a small amount of ether or from ether–hexane, giving methyl 2-*O*-acetylanhydroterminolate (0·6 g.) as prisms, m. p. 185—187°, [α] +1° (*c* 1·04) (Found: C, 73·4; H, 9·6. $C_{33}H_{50}O_8$ requires C, 73·0; H, 9·3%).

Methyl Tri-O-*acetyl*-6-*chlorodihydro*-5-*hydroxy*-12-*oxoarjunolate*.—Methyl tri-*O*-acetylanhydroterminolate, isolated as an amorphous solid by acetylation of pure methyl terminolate (1·4 g.), was treated at 100° for 3 hr. with acetic acid (25 c.c.) containing 30% hydrogen peroxide (2 c.c.). The product was isolated by pouring the solution into water and presumably consisted of methyl tri-*O*-acetyldihydroanhydroepoxy-12-oxoterminolate but it was not found possible to crystallise this or its hydrolysis product. The crude acetate was therefore dissolved in dry chloroform, and a stream of hydrogen chloride was passed in during 1 hr. After a further 2 hr. the solvent was removed under reduced pressure and the residue of the *chlorohydrin* (0·93 g.) readily crystallised from methanol or aqueous methanol in prisms, m. p. 184°, [α] −73° (*c* 0·74) (Found: C, 63·5; H, 7·8; Cl, 5·2. $C_{37}H_{55}O_{10}Cl$ requires C, 63·9; H, 8·0; Cl, 5·1%). The compound was recovered unchanged after attempted oxidation with chromic oxide–acetic acid–sulphuric acid for 5 days at room temperature.

We thank Dr. G. D. Meakins for determining the infrared spectra of several of the compounds described.

THE UNIVERSITY, NOTTINGHAM. [*Received, May 23rd,* 1956.]

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861. *The Chemistry of Extractives from Hardwoods. Part XXVIII.* The Occurrence of* 3 : 4 : 3′ : 5′-*Tetrahydroxy- and* 3 : 4 : 5 : 3′ : 5′-*Pentahydroxy-stilbene in* Vouacapoua *species.*

By F. E. KING, T. J. KING, D. H. GODSON, and L. C. MANNING.

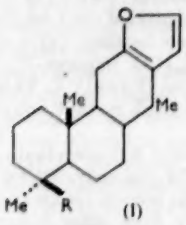
The heartwood of *Vouacapoua macropetala* and of *V. americana* contains 3 : 4 : 3′ : 5′-tetrahydroxystilbene, which was isolated by ether-extraction. Also present in *V. macropetala* is the 3 : 4 : 5 : 3′ : 5′-pentahydroxystilbene. The structures of these new products were deduced from the hydroxybenzoic acids obtained on oxidation of the fully acetylated compounds, and the constitution attributed to the tetrahydroxystilbene was confirmed by a synthesis of the tetramethyl ether from 3 : 5-dimethoxybenzaldehyde and 3 : 4-dimethoxyphenylacetic acid.

THE principal petroleum-soluble constituent of the wood from the South American *Vouacapoua americana* and *V. macropetala* consists of a diterpene ester, methyl vouacapenate (I; R = CO_2Me), and it occurs in the latter species together with vouapenyl acetate (I; R = CH_2·OAc).[1] The composition of the products obtained by

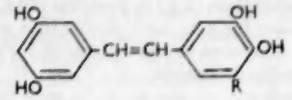
* Part XXVII, preceding paper.

[1] King, Godson, and King, *J.*, 1955, **1**, 117.

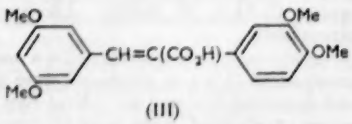
continuing the extraction with ether has now been examined and it has been shown that both species contain the hitherto unknown 3 : 4 : 3′ : 5′-tetrahydroxystilbene (II; R = H). The ether extract of *V. macropetala* contains also 3 : 4 : 5 : 3′ : 5′-pentahydroxystilbene (II; R = OH), the most fully substituted natural stilbene so far encountered. It is of interest that 3 : 5-dihydroxystilbene (pinosylvin) together with its methyl ethers constitutes



(I)



(II)



(III)

the sole example of this series found in the coniferous woods in which it is strictly confined to *Pinus* species.[2] On the other hand, the more heavily substituted compounds, *e.g.*, 4′-hydroxy-3 : 5-dimethoxystilbene (pterostilbene),[3] 2 : 4 : 3′ : 5′-tetrahydroxystilbene,[4] and its 4-substituted derivative chlorophorin,[5] occur in various unrelated genera of dicotyledonous trees, although all examples so far recorded are derivatives of 3 : 5-dihydroxystilbene, a fact denoting a common phytochemical origin.

3 : 4 : 3′ : 5′-Tetrahydroxystilbene was isolated from the brown resin extracted by ether from the light petroleum-exhausted wood by leaching it with hot water. The compound $C_{24}H_{12}O_4$ obtained by concentrating the aqueous solution and further crystallisation exhibited reducing properties and the usual colour reactions, *e.g.*, transient blue violet with ferric chloride, characteristic of a polyhydric phenol. It formed a crystalline tetra-acetate, tetrabenzoate, and tetramethyl ether all of which retained the reactivity to aqueous bromine and potassium permanganate of the parent compound. Light absorption of the phenol and of its methyl ether in the ultraviolet region denoted a stilbene structure.

Oxidation of the tetra-acetate and the tetramethyl ether with chromic oxide gave inseparable products, but paper chromatography [6] of the hydrolysed mixture from the acetate oxidation showed, by comparison with authentic specimens, the presence of 3 : 5- and of 3 : 4-dihydroxybenzoic acid. However, the method of identification made it desirable to seek further support for the structure, for example, by synthesis of the tetramethyl ether. A derivative of rhapontigenin (3 : 5 : 3′-trihydroxy-4′-methoxystilbene), isolated as a glycoside from the roots of *Rhus pontifica* and other species,[7] has been synthesised [8] by condensation of *iso*vanillin with sodium 3 : 5-dihydroxyphenylacetate, but analogous condensations employing veratric or protocatechuic aldehyde failed to yield crystalline products. However, by the action of 3 : 5-dimethoxybenzaldehyde on sodium 3 : 4-dimethoxyphenylacetate, small quantities of the stilbene-carboxylic acid (III) were obtained, and decarboxylation of the product yielded the difficultly crystallisable 3 : 4 : 3′ : 5′-tetramethoxystilbene, identical with the corresponding ether of the natural product. The well-characterised trinitrobenzene derivatives also were indistinguishable.

The ether extracts of *V. americana* gave no other purifiable compound, but by acetylation of the crude extract from *V. macropetala* a further crystalline product was isolated, which was unsaturated to bromine and permanganate, and corresponded in molecular formula with a penta-acetoxystilbene. Benzoylation of the crude extract gave a corresponding benzoate. Hydrolysis of the penta-acetate in an inert atmosphere gave the

[2] Erdtman, "Progress in Organic Chemistry," Butterworths, London, 1952, Vol. I, p. 22.
[3] Spath and Schlager, *Ber.*, 1940, **73**, 881.
[4] Barnes and Gerber, *J. Amer. Chem. Soc.*, 1955, **77**, 3259; Takaoka, *J. Fac. Sci., Hokkaido Imp. Univ.*, 1940, **3**, 1.
[5] King and Grundon, *J.*, 1949, 3348; 1950, 3547.
[6] Bate-Smith and Westall, *Biochem. Biophys. Acta*, 1950, **4**, 428.
[7] Kawamura, *J. Pharm. Soc. Japan*, 1938, **58**, 83, 405.
[8] Takaoka, *Proc. Imp. Acad. (Tokyo)*, 1940, **16**, 408.

pentahydroxystilbene in yellowish prisms, very readily oxidised in alkaline solution and giving an intense transient blue-black colour with ferric chloride.

Oxidation of the acetate with potassium permanganate, followed by mild hydrolysis, formed a mixture of acids which were separated by crystallisation into 3 : 5-dihydroxybenzoic acid and gallic acid, both of which were identified by m. p. and mixed m. p. They were converted into the methyl ethers which were also identified by comparison with authentic specimens. The structure of the parent phenol was thereby established as 3 : 4 : 5 : 3′ : 5′-pentahydroxystilbene (II; R = OH).

Experimental

Light petroleum was of b. p. 60—80°.

3 : 4 : 3′ : 5′-*Tetrahydroxystilbene.*—The powdered wood (3—3·2 kg.) which had previously been extracted with light petroleum was exhausted with boiling ether during 48 hr. The extracts were evaporated and the light petroleum-soluble part was removed with that solvent. Treated in this way *V. americana* gave 36 g. of a black gum and *V. macropetala* 56 g. of brown resin. The extract from *V. americana* was leached with boiling water (3 × 300 c.c.), and the extract filtered and concentrated (vacuum) to 50 c.c. After 24 hr. at 0° the *tetrahydroxystilbene* (1·6 g.) separated as a grey crystalline powder. Similar treatment of the extract from *V. macropetala* gave 7 g. of the phenol. Purification of the product from either water or methanol–benzene gave almost colourless plates, m. p. 229° (rapid heating, decomp.) (Found: C, 69·0; H, 4·9. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%), light absorption max. (in EtOH) at 330 mμ (ε 27,600). The ferric chloride colour was a transient blue-violet. The *tetra-acetate* obtained with acetic anhydride–pyridine separated from methanol in colourless needles, m. p. 114—115° [Found: C, 63·9; H, 4·5; OAc, 41·7%; *M* (Rast), 395. $C_{22}H_{20}O_8$ requires C, 64·1; H, 4·9; 4OAc, 42·5%; *M*, 412]. The *tetrabenzoate* crystallised from acetone–methanol as colourless needles, m. p. 123—124° [Found: C, 76·0; H, 4·6%; *M* (Rast), 675. $C_{42}H_{28}O_8$ requires C, 76·3; H, 4·3%; *M*, 660].

Oxidation of the Tetra-acetoxystilbene.—The acetate (50 mg.) with acetic acid (30 c.c.) containing chromic oxide (35 mg., 1·1 mol.) was kept for 15 min. at room temperature and then poured into water. The products were extracted with ether, and the extract was evaporated; the residue was then warmed for a short time with excess of dilute aqueous sodium hydroxide and again acidified and extracted with ether (5 × 15 c.c.). The residues were examined by paper chromatography.[8] The mobile phase first used was butanol–acetic acid–water (4 : 1 : 5), and development with ferric chloride showed a single green spot corresponding in R_F value to protocatechuic acid. Development of a similar chromatogram with diazotised benzidine gave a pink spot corresponding to that given by 3 : 5-dihydroxybenzoic acid. Direct chromatographic comparison of the degradation products with authentic samples of both dihydroxybenzoic acids in butanol–acetic acid–water and in *m*-cresol–water confirmed the identification of the oxidation products. No other spots could be detected.

3 : 4 : 3′ : 5′-*Tetramethoxystilbene-α-carboxylic Acid.*—Sodium 3 : 4-dimethoxyphenylacetate[9] (1·77 g.) and 3 : 5-dimethoxybenzaldehyde (1·4 g., 1·1 mol.) (prepared by oxidation of the corresponding alcohol[10] with chromic oxide in pyridine) were heated with acetic anhydride (20 c.c.) at 175—180° (bath-temp.) for 8 hr. and then the acetic anhydride was removed *in vacuo*. The residual gum was dissolved in ether and washed with dilute acid. Removal of the solvent left a gum which crystallised when boiled with light petroleum. The acid was purified from methanol, from which it separated in yellow needles (1·3 g.), m. p. 167—168° (Found: C, 66·7; H, 6·1. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·85%).

3 : 4 : 3′ : 5′-*Tetramethoxystilbene.*—(*a*) Methylation of the tetrahydroxystilbene (3 g.) with methyl sulphate (7·5 g.) and potassium carbonate (15 g.) in boiling acetone for 20 hr. gave, after filtration and removal of the acetone, a brown oil (3·6 g.). Repeated distillation of the residue gave a pale yellow oil, b. p. 180—190°/0·1 mm., which, after chromatography on alumina in light petroleum–benzene followed by refrigeration under light petroleum, gave the *tetramethoxystilbene* (1 g.) as colourless needles, m. p. 68—69° (Found: C, 72·0; H, 6·6; OMe, 41·2. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7; 4OMe 41·2%), light absorption max. (in EtOH) at 325 mμ (ε 31,000).

(*b*) The pure stilbenecarboxylic acid above (0·65 g.) was heated in boiling quinoline (20 c.c.)

[9] Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1126.
[10] Adams, Harfenist, and Loewe, *ibid.*, 1949, **71**, 1627.

with copper bronze (2 g.) for 10 min. When cool the mixture was diluted with ether (100 c.c.) and filtered. The filtrate was exhaustively extracted with dilute hydrochloric acid and aqueous sodium hydroxide, dried, and distilled. Repeated distillation gave an oil which was covered with light petroleum and then, after some time, crystallised. Purification from methanol gave the stilbene as needles, m. p. and mixed m. p. 68—69° (Found: C, 72·0; H, 6·5%), light absorption max. (in EtOH) at 325 mμ (ε 31,000).

Both specimens of the stilbene gave identical *adducts* with trinitrobenzene in ethanol, as maroon-coloured prisms, m. p. and mixed m. p. 109—110° (Found, for natural compound: C, 55·8; H, 4·6; for synthetic compound C, 56·3; H, 4·3. $C_{18}H_{20}O_4,C_6H_3O_6N_3$ requires C, 56·1; H, 4·5%).

3 : 4 : 5 : 3′ : 5′-*Penta-acetoxystilbene*.—The crude ether extract of *V. macropetala* (56 g.) was acetylated in pyridine at 100° for 30 min. The solution was evaporated under reduced pressure, leaving a brown residue which crystallised when warmed with methanol. Recrystallisation from acetone–methanol (charcoal) gave the penta-acetate (16·9 g.) as colourless plates, m. p. 173—174° [Found: C, 61·4; H, 4·6; OAc, 44·4%; *M* (Rast), 441. $C_{24}H_{22}O_{10}$ requires C, 61·3; H, 4·7; 5 OAc, 45·7%; *M*, 470].

3 : 4 : 5 : 3′ : 5′-*Pentahydroxystilbene*.—The penta-acetate (1 g.) was hydrolysed under nitrogen for 30 min. at room temperature with 2% methanolic potassium hydroxide (100 c.c.). The excess of alkali was then neutralised with acetic acid, and the solution evaporated. The residue was dissolved in water and extracted with ethyl acetate, and the extract was evaporated. The *pentahydroxystilbene* thus obtained crystallised from a small amount of water in pale yellow needles, m. p. *ca.* 245° (decomp., evac. capillary) (Found, on an air-dried sample: C, 57·0; H, 5·4. $C_{14}H_{12}O_5,2H_2O$ requires C, 56·75; H, 5·4. On a sample dried at 100°: C, 64·2; H, 4·8. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·65%). The *pentabenzoate* prepared in pyridine crystallised from chloroform–methanol in needles, m. p. 165—166° (Found: C, 75·4; H, 4·3. $C_{49}H_{32}O_{10}$ requires C, 75·4; H, 4·1%). The same benzoate could also be obtained in small yield by benzoylation in pyridine of the crude timber extract.

Oxidation of the Penta-acetoxystilbene.—The penta-acetate (4·8 g.) in acetone (75 c.c.) was treated at room temperature with potassium permanganate (10 g.). When the permanganate had been destroyed the acetone was evaporated and the residue was warmed for a short time with dilute alkali to complete the hydrolysis of the acetoxy-group. The suspension was then acidified by the passage of excess of sulphur dioxide. Exhaustive extraction of the solution with ether followed by removal of the solvent afforded a brown acidic residue (2·5 g.). This residue was warmed with water (5 c.c.), and the solid which separated in the cold was recrystallised from water to give nearly colourless rods, m. p. 232—234° raised to 233—235° by admixture with authentic 3 : 5-dihydroxybenzoic acid (m. p. 236—238°). The water-soluble fraction of the crude oxidation product was isolated by evaporation and crystallised from ethyl acetate as light brown flat prisms, m. p. 245—250° (effervescence), giving colour reactions with ferric chloride and potassium cyanide identical with those shown by gallic acid.

Both acids were methylated with methyl sulphate in acetone in the presence of potassium carbonate and after hydrolysis of any ester produced gave respectively: 3 : 5-dimethoxybenzoic acid as colourless needles (from ethyl acetate), m. p. and mixed m. p. 185—186° (lit., 185—186°) (Found: C, 59·6; H, 5·7; OMe, 34·2. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5; 2OMe, 34·3%); and trimethylgallic acid as colourless needles (from ethyl acetate–light petroleum), m. p. and mixed m. p. 169—170° (lit., 168°) (Found: C, 56·1; H, 5·6; OMe, 43·8. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7; 3OMe, 43·8%).

One of the authors (D. H. G.) thanks the Department of Scientific and Industrial Research for a Maintenance Allowance.

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862. *The Simple Fluorides of Iridium, including the New Trifluoride.*

By P. L. Robinson and G. J. Westland.

The hexafluoride and tetrafluoride of iridium have been re-investigated, and improved methods of preparing the latter developed. Some new reactions of the hexafluoride are described. These have led to the isolation of new compounds, including $IrF_5.SF_4$, $IrF_5.SO_2$, $(NO)_2IrF_6$, $(NO_2)_2IrF_6$, $(NO)_2IrF_5$, and $(NO_2)_2IrF_5$. No evidence of the formation of a pentafluoride has been secured; but the trifluoride, hitherto unknown, has been prepared and characterised. The iridium fluorides are briefly considered in relation to the simple fluorides of other members of Group VIII.

Observations by Hepworth, Robinson, and Westland,[1] during isolation of the hexafluoroiridates(v) and hexafluoroiridates(iv), prompted a re-investigation of the simple fluorides of iridium. The available information about them is a paper by Ruff and Fischer,[2] published twenty-seven years ago; in this the hexafluoride, IrF_6, and tetrafluoride, IrF_4, were characterised and the possibility of a still lower fluoride was mooted. In the work described here, the formation of the hexa- and tetra-fluoride has been confirmed and both have now been extensively studied; in addition the occurrence of a third fluoride has been established and it is shown to be the trifluoride, IrF_3.

Iridium Hexafluoride.—This is best prepared directly from the elements at 300—400°, is bright yellow, melts at 44° and boils at 53°. The vapour is dense and deep yellow and is stable up to red heat. It is the only compound in which iridium is unequivocally in the sexavalent condition, and measurements of its magnetic moment, made for us by Professor Nyholm, are in conformity with an octahedral distribution of the bonds about the metal, and show that Hund's rules of maximum multiplicity are obeyed in this valency state. Table 1 illustrates the outer electronic configuration of iridium(vi) and its similarity to those of rhenium and osmium in the isoelectronic ReF_6^{2-} and OsF_6^- ions (the octahedral shape of the molecule has recently been deduced from its infrared spectrum [3]). The effective magnetic moment as measured, 3·3 B.M., is appreciably lower than the value calculated, 3·88 B.M., owing presumably to a Russell–Saunders type of coupling between the resultant spin and orbital angular momenta. The presence of this L–S coupling would be established by a temperature-susceptibility study of the compound.

Table 1.

Compound	Valency	Outer electronic configuration 5*d*	6*s*	6*p*	Magnetic moment (B.M.) Found	Calc.
K_2ReF_6 ...	IV	↓↓↓↓↓ ↑↑↑	↑↓	⟨↑ ↑ ↑⟩	3·2 [a]	3·88
$KOsF_6$	V	↓↓↓↓↓ ↑↑↑	↑↓	⟨↑ ↑ ↑⟩	3·2 [b]	3·88
IrF_6	VI	↓↓↓↓↓ ↑↑↑	↑↓	⟨↑↓ ↑ ↑⟩	3·3 [c]	3·88

[a] Weise, *Z. anorg. Chem.*, 1956, **283**, 377. [b] Hepworth, Robinson, and Westland, *J.*, 1954, 4268. [c] Present work.

Although very stable, the hexafluoride is extremely active chemically and behaves as a strong fluorinating agent, in which respect it is comparable with osmium octafluoride (see Ruff and Tschirch [4]). Contrary, however, to the findings by Ruff and Fischer [2] this reactivity does not prevent the hexafluoride from being handled in glass at temperatures

[1] Hepworth, Robinson, and Westland, *J.*, 1954, 4269.
[2] Ruff and Fischer, *Z. anorg. Chem.*, 1929, **179**, 161.
[3] Mattraw, Hawkins, Carpenter, and Sabol, *J. Chem. Phys.*, 1955, **23**, 985.
[4] Ruff and Tschirch, *Ber.*, 1913, **46**, 929.

below 150°, provided the glass has been rigorously dried. In this connection, we have found no evidence for the oxyfluoride, $IrOF_4$, which Ruff and Fischer thought was formed when the hexafluoride is left in contact with glass. All our experiments which might conceivably have led to the isolation of such a substance, for example, keeping the hexafluoride in a glass vessel for several months, and repeated fluorination of iridium dioxide, IrO_2, failed to give a sign of an oxyfluoride.

Since sexavalent iridium readily acquires electrons, the reactions of the hexafluoride naturally involve its reduction to one of the lower valency states.

Quinquevalent iridium, as found in the anion IrF_6^-, is the stable state of the element in a liquid fluoride medium, such as bromine trifluoride. When the fluoride solvent is itself susceptible of further fluorination, the iridium hexafluoride is reduced to the quinquevalent condition; thus, for example, Hepworth, Robinson, and Westland [5] have shown that in selenium tetrafluoride the product is the "acid" SeF_3,IrF_6. We find a similar reaction takes place even more readily with the sulphur tetrafluoride, SF_4, recently made available.[6] In this instance, the resulting material has the empirical composition IrF_5,SF_4, though whether it should have a formulation analogous to the corresponding selenium compound must await more evidence on the existence of the SF_3^+ cation. Liquid sulphur dioxide also appears to bring about a reduction to the quinquevalent condition, giving a product represented by IrF_5,SO_2.

Quadrivalent iridium is the result of most reductions of the hexafluoride, the compound isolated depending upon the reducing agent employed. Thus hydrogen, chlorine, and iodine under appropriate conditions produce the tetrafluoride, IrF_4, being themselves fluorinated in the process. On the other hand, both nitric oxide and gaseous dinitrogen tetroxide combine readily with the hexafluoride to give nitrosonium hexafluoroiridate(IV), $(NO)_2IrF_6$, and nitronium hexafluoroiridate(IV), $(NO_2)_2IrF_6$, which separate in the pure condition as pale yellow and white solids respectively. That these compounds are nitrosonium and nitronium salts is demonstrated by their reaction with water to form a mixture, in the first instance, of nitrous acid and, in the second, of nitric acid, with hexafluoroiridic acid, H_2IrF_6. The mechanism of their formation is most probably an electron-transfer from the oxide to the fluoride; certainly, although these were looked for in the experiments, nitrosyl fluoride, nitryl fluoride, and iridium tetrafluoride were not detected. Thermal degradation of the salts results in the loss of a fluorine atom from each and in compounds having the compositions $(NO)_2IrF_5$ and $(NO_2)_2IrF_5$ respectively.

Liquid sulphur trioxide also reacts, though slowly, with iridium hexafluoride to give an ill-defined, dark blue product with a composition approximating to $IrF_4,3SO_3$.

We investigated qualitatively a variety of other reactions of the hexafluoride; in many of these, reduction reaches the stage of the free element which manifests itself in the *X*-ray powder photographs. Thus carbon monoxide and ammonia each reduced it vigorously to the metal. Phosphorus trifluoride, which we had hoped would co-ordinate to give an identifiable derivative, produces dark green solids of variable composition always heavily contaminated with the free element.

Iridium Tetrafluoride.—This compound is to be regarded as the parent of the hexafluoroiridates(IV). Methods for its preparation all involve reduction of the hexafluoride. Ruff and Fischer [2] used iridium metal in a sealed quartz tube at 150° for this purpose; the method gives an almost quantitative yield. However, a little above 200° the hexafluoride attacks glass readily and is thereby reduced to tetrafluoride; the temperature at which this occurs is quite well defined and the reaction forms the most convenient way of preparing the tetrafluoride. Finally, we find that the pure tetrafluoride is formed, though in poor yield, in the photolysis of iridium hexafluoride by ultraviolet light.

When pure, iridium tetrafluoride is a yellow solid, melting at 106—107° to a dark yellow liquid which boils above 300°. It is very sensitive to moisture, being rapidly hydrolysed to hydrated iridium dioxide and hydrofluoric acid; it is a poor fluorinating agent, in which respect it rather resembles ruthenium pentafluoride, RuF_5. Like the hexafluoride, it is

[5] Hepworth, Robinson, and Westland, *Chem. and Ind.*, 1955, 1516.
[6] Brown and Robinson, *J.*, 1955, 3147.

reduced to the metal by carbon monoxide; but it does not react with nitric oxide to give a nitrosonium salt.

Iridium Trifluoride.—Ruff and Fischer [2] noticed that when iridium tetrafluoride was strongly heated, their black residues varied in composition, the iridium : fluorine atomic ratio ranging from 1 : 1 to 1 : 4. An examination of the formulæ of the lower fluorides of Group VIII, given in Table 2, shows *two* trifluorides in the iron and *three* in the ruthenium triad; and we early felt that, should there be a third fluoride of iridium, it ought to belong to this class. Our thermal decompositions of the tetrafluoride in glass within a certain temperature range do actually give black solids which are pure iridium trifluoride, but the method is tedious and the yields small. By heating iridium tetrafluoride in an atmosphere of sulphur tetrafluoride a slightly better yield of trifluoride is more easily obtained. With a view to further improving the yield other reactions were examined, but all give impure products; among these may be cited the reaction of iridium on iridium hexafluoride, and the reduction of iridium tetrafluoride severally with iodine, sulphur, and hydrogen.

Iridium trifluoride is a brownish-black to black solid, insoluble in and unaffected by water, and attacked only slowly by concentrated acids and alkalis. In these respects it resembles the ruthenium and the rhodium trifluoride with which it is isostructural; the rhombohedral unit cell contains two molecules and has the dimensions $a = 5{\cdot}42$ Å, $\alpha = 54{\cdot}3°$. Structural details will be published elsewhere.[7] Thermally the trifluoride is not very stable; above 250° it begins to lose fluorine and give iridium metal. This probably accounts for the variable composition observed by Ruff and Fischer.

TABLE 2.*

FeF_3	CoF_3	NiF_3
FeF_2	CoF_2	
		$[PdF_3]$
RuF_5	RhF_3	PdF_2
	RhF_4	
RuF_6: m. p. 106°; b. p. 313°		
	IrF_3	
$[OsF_4]$	IrF_4: m. p. 106—107°; b. p. >300° [a]	PtF_4
OsF_6: m. p. 74·5°; b. p. 200° [a]	IrF_6: m. p. 44·4°; b. p. 53° [d]	
OsF_8: m. p. 34°; b. p. 47° [b]		

* Compounds given in brackets cannot be held to be established with certainty.

[a] Hepworth, Ph.D. Thesis, Durham, 1956, p. 55. [b] Ruff and Tschirch, *Ber.*, 1913, **46**, 929. [d] Present work. [d] Ruff and Fischer, *Z. anorg. Chem.*, 1929, **179**, 161.

We have sought to settle the question of the existence of a pentafluoride of iridium—the hypothetical parent of the hexafluoroiridates(v)—but all our evidence points to its absence from the series; as with osmium the simple pentafluoride does not seem to occur.

The now known simple fluorides of the Group VIII elements are listed in Table 2. When a group is set out in this way resemblances between the elements are generally to be sought in a vertical direction though these are not particularly marked in Group VIII. In this respect, however, the new iridium trifluoride provides a link between the third and earlier triads. In its fluorine chemistry iridium also exhibits certain similarities to the diagonally placed ruthenium and to the horizontally disposed osmium. In particular, these elements all form isostructural complex fluorides of the types $K_2M^{IV}F_6$ and $KM^{V}F_6$, and we can trace this relationship back to likenesses between the simple fluorides. For instance, iridium tetrafluoride and ruthenium pentafluoride display a marked similarity in chemical properties and, as an examination of Table 2 shows, the relation extends to some of their physical properties. Again, the essentially covalent iridium hexafluoride lies physically and chemically closer to osmium octafluoride than it does to osmium hexafluoride.

EXPERIMENTAL

Preparation of Iridium Hexafluoride.—To prepare iridium hexafluoride Ruff and Fischer [2] fluorinated iridium metal in a fluorite tube and fractionated the product in a quartz apparatus.

[7] Hepworth, Jack, and Westland, unpublished work.

We found that the hexafluoride was indifferent to Pyrex glass up to about 150°, provided the surface had been rigorously freed from moisture, and that it could be conveniently handled in this glass. These conditions were achieved by baking-out the apparatus at 300—400° at about 10^{-3} mm., and having well-cooled "guard" traps. Fluorine, freed from hydrogen fluoride by passage over sodium fluoride pellets followed by a trap at −180°, and diluted with nitrogen, was passed over iridium in an alumina boat at 300—400°. The temperature at which reaction began depended on the history and state of division of the metal. The bright yellow hexafluoride vapour was collected at −65° in a Pyrex-glass train, and there subjected to a trap-to-trap distillation in a vacuum. Still under a vacuum, it was either transferred to a break-seal vessel for storage, or used directly in an all-glass apparatus. The absence of greased joints and taps was essential, since we found that iridium hexafluoride attacked, and suffered contamination from, all the greases tried.

Preparation of Iridium Tetrafluoride.—(a) *Reduction of iridium hexafluoride by iridium metal.* This was effected by carrying the fluoride in a slow stream of dry nitrogen over the metal in a nickel boat in a heated Pyrex-glass tube. At 100° reduction was slow, but between 150° and 170° it was much quicker and practically quantitative. The tetrafluoride condensed to a yellow-brown oil beyond the heated zone, and was purified by fractional distillation at 120—140°/10^{-3} mm. The vapour passed directly into a solid at the cooled surface; this solid, when pure, consisted of yellow, needle-shaped crystals. The valency of the iridium was established by allowing it to react with potassium iodide (2%) in N-sulphuric acid and estimating the iodine with thiosulphate. One equivalent of iodine was liberated per equivalent of iridium which was itself reduced to the tervalent state, indicating a valency of four in agreement with the value found by Ruff and Fischer.[3] The crystalline material melted sharply at 106—107° to a dark yellow liquid which, on cooling, set to a glass that crystallised only on very long storage. The b. p. was found to be above 300°; a more precise estimate was impossible because of decomposition and attack on the glass. Pure iridium tetrafluoride could be kept indefinitely in glass under dry air, but in moist air it fumed and was rapidly hydrolysed to a hydrated oxide and hydrofluoric acid. With excess of water, it reacted vigorously to form a purple solution containing colloidal oxide and hydrofluoric acid.

(b) *Reduction of iridium hexafluoride by glass.* This was attained by passing the fluoride through a heated Pyrex tube in a slow stream of dry nitrogen. Below 190° there was no visible attack or decomposition; but, at 250°, an almost quantitative yield of the tetrafluoride was obtained, again as a yellow-brown oil. This was purified as already described (Found: Ir, 71·4. Calc. for IrF_4: Ir, 71·7%). The silicon tetrafluoride, boron trifluoride, and alkali fluorides simultaneously formed were easily separated from the product.

(c) *Photolysis of iridium hexafluoride.* 1 G. portions of the fluoride were sealed in transparent silica bulbs furnished with break-seals. These were irradiated at the ambient temperature for 6 days with ultraviolet light from a mercury-vapour lamp at a distance of 6 in. The yield of yellow crystalline solid was poor (30% conversion), but was pure tetrafluoride. The unchanged iridium hexafluoride, silicon tetrafluoride, and oxygen were removed under a vacuum. Presumably the photolysis, $IrF_6 \longrightarrow IrF_4 + F_2$, released fluorine which slowly reacted with the silica ($SiO_2 + 2F_2 \longrightarrow SiF_4 + O_2$).

Preparation of Iridium Trifluoride.—(a) *Reduction of iridium tetrafluoride by glass.* This was brought about by heating the fluoride in a glass vessel under dry air. At 280° there was only a slight darkening of the liquid and inappreciable decomposition, but at 430—450° a solid appeared and continued to be formed. After 12—18 hr., the resulting black mass was found to contain, besides an insoluble portion, some residual tetrafluoride. The latter was removed by washing the whole with water followed by 15% hydrochloric acid until the runnings were no longer coloured; afterwards water, alcohol, and ether were used, and finally the solid was dried at 40°. It proved to be *iridium trifluoride* (Found: Ir, 77·0. IrF_3 requires Ir, 77·2%). The identity of the new compound was settled by Debye *X*-ray powder photographs which showed it to be free from iridium metal and dioxide, and to be isostructural with palladium and rhodium trifluorides. The lattice was rhombohedral and contained two molecules per unit cell with $a = 5{\cdot}42$ Å and $\alpha = 54{\cdot}3°$.

(b) *Reduction of iridium tetrafluoride by sulphur tetrafluoride.*[6] This was effected by passing the vapour of sulphur tetrafluoride over the iridium compound in a heated glass tube. At about 100° the iridium tetrafluoride absorbed some sulphur tetrafluoride, becoming brown; then, at 350—400°, a rapid reaction produced brownish-black iridium trifluoride, only slightly contaminated with the tetrafluoride. The latter was removed as before. The yield was better, without apparent decrease in purity. Furthermore, sulphur tetrafluoride appeared to

inhibit the decomposition of iridium trifluoride to metal and fluorine, for even heating to 550—600° in sulphur tetrafluoride left the compound largely intact.

In the absence of iridium tetrafluoride, the trifluoride was decomposed into its elements when heated above 250° in alumina under dry air. The decomposition was slow at 250°, but became faster before 450° was reached, being then complete in 30 min. Hence, in the preparation, the necessity for stopping heating before all the iridium tetrafluoride was spent, and for controlling the temperature to avoid either a too tedious preparation or a product adhering to the glass. It has been mentioned that the trifluoride was insoluble in water and dilute acids: even with concentrated acids attack was slow.

The Supposed Oxyfluoride of Iridium.—(a) *Action of iridium hexafluoride on glass.* When handling iridium hexafluoride in glass, a careful watch was kept for non-volatile residues. These, usually cream to pale yellow, were always in insignificant quantities—quite insufficient for characterisation. When treated with water, traces of gas, probably oxygen, were evolved and colourless to pale yellow solutions were left. This suggested that these residues, and probably the material which Ruff and Fischer supposed to be $IrOF_4$, were complex salts of quinquevalent iridium of the type $M^{I}IrF_6$(v), resulting, very feasibly, from the reaction between iridium hexafluoride and the alkali of the glass. Keeping the hexafluoride in a well-dried vessel at room temperature for several months did not appreciably increase the residues, nor did limited additions of moisture stimulate their formation. The effect of the latter was to produce at first some tetrafluoride and, finally, hydrated iridium oxide and hydrogen fluoride.

(b) *Fluorination of iridium dioxide.* Iridium dioxide was prepared by fusing sodium hexachloroiridate(IV) with fusion mixture in a platinum dish, extracting the melt with hot water, and washing the black residue with more hot water followed by dilute hydrochloric acid to remove adsorbed alkali. Subsequent heating for 4 hr. at 600° in a stream of dry oxygen yielded pure anhydrous iridium dioxide, as was shown by its Debye *X*-ray photograph. Fluorine, very well diluted with oxygen, was passed over this material in a nickel boat in a transparent silica tube. The temperature was slowly raised without evidence of reaction until 350°; at this point the oxide was rapidly and completely converted directly into hexafluoride.

Reactions of Iridium Hexafluoride.—(a) *Hydrogen.* The gas, dried by cooling to −180°, reacted quietly with iridium hexafluoride vapour at 60° giving yellow-brown, oily droplets of the tetrafluoride and hydrogen fluoride. At 100°, however, the reduction proceeded further and more rapidly, producing metallic iridium, as shown by an *X*-ray of the black product. There did not appear to be an intermediate stage in the reduction from the four to the zero valency state.

(b) *Iridium metal.* The residue remaining in the boat after preparation of iridium tetrafluoride (see above) was principally unchanged metal together with a little trifluoride. But when the reaction was carried out at about 500° in an all-nickel apparatus, and the product was allowed to cool in iridium hexafluoride vapour, the material contained up to 50% of the trifluoride. A complete conversion of the metal into trifluoride by this reaction was probably impossible; first, because an initial protective layer of the trifluoride effectively hindered further attack and, secondly, because this trifluoride layer, in the presence of a large excess of iridium hexafluoride, was further fluorinated to the tetrafluoride: thus iridium metal and tetrafluoride tended to be the ultimate products.

(c) *Halogens.* (i) Chlorine, diluted (1 : 1) with dry nitrogen, reacted quietly with iridium hexafluoride vapour at 55—60° to give dark green, oily droplets and a chlorine fluoride, the latter being carried out of the reaction zone by the chlorine–nitrogen stream. Distillation of the liquid in a vacuum at 120—140° yielded a chlorine-free sublimate of yellow iridium tetrafluoride.

(ii) Purified dry iodine, in amount calculated for $5IrF_6 + I_2 \longrightarrow 5IrF_4 + 2IF_5$, gave, at room temperature, a product identical in appearance with iridium tetrafluoride; however, it retained traces of iodine pentafluoride even after distillation at 10^{-3} mm. It reacted vigorously with more iodine at 120°; the black products, after being heated in a vacuum at 100° for 24 hr., varied in composition. One specimen approximated to $Ir_2F_6I_2$ (Found: Ir, 43·0; F, 11·9. Calc. for $Ir_2F_6I_2$: Ir, 43·8; F, 12·9%) and the *X*-ray photograph showed neither iridium trifluoride nor metal, indeed no identifiable pattern. It was insoluble in water and dilute hydrochloric acid, but dissolved in aqueous potassium hydroxide forming a chocolate-coloured solution which became reddish-violet when boiled. Heated dry to 400°, it gave iridium metal. Since both iodine and iridium hexafluoride dissolve in iodine pentafluoride, solutions of each were mixed at room temperature, and, after the supernatant liquid had been boiled, the precipitate was removed and heated to 150° in a vacuum. The solid was dark purple, slightly

hygroscopic, decomposed to metal at 400°, and approximated to IrF_3,0·2I (Found: Ir, 70·5; F, 20·3. Calc. for IrF_3,0·2I: Ir, 70·1; F, 20·7%), but could not be identified by *X*-ray investigation.

(d) *Sulphur trioxide.* Specially prepared sulphur trioxide which had been kept over phosphoric oxide for several hours was purified by repeated trap-to-trap distillation and condensed on to solid iridium hexafluoride. The latter proved to be insoluble and the ensuing reaction slow as the solid changed through yellow, green, and brown to blue. After 1—2 hours' refluxing and removal of the sulphur trioxide in a vacuum, a deep blue solid with the composition IrF_4,3SO_3 was left (Found: Ir, 38·0; SO_3, 47·1. IrF_4,3SO_3 requires Ir, 37·9; SO_3, 47·2%). The iridium had a valency of four. The *compound* was hygroscopic in moist air, and in water dissolved to give a deep blue solution which slowly became blue-violet and, when boiled, reddish-violet. Dwyer and Gyarfas[8] obtained dark blue, ill-defined solids from oxidised solutions of iridium(III) sulphate, perchlorate, and nitrate and suggested that the colours were due to the $[IrO{\cdot}OH]^+$ ion (blue-violet) and IrO^{++} ion (reddish-violet). We were able to show that iridium was present as a cation in the deep blue solution by passing it through an exchange resin (hydrogen-charged): the blue material was absorbed. In concentrated sulphuric acid the blue colour was stable for several days.

(e) *Sulphur tetrafluoride.* Iridium hexafluoride reacted quietly with liquid sulphur tetrafluoride at −60° to give a precipitate which, after the removal of supernatant reactant under a vacuum at room temperature, appeared as a light brown powder (Found: Ir, 48·5; F, 42·1; S, 8·5. IrF_6,SF_4 requires Ir, 48·7; F, 43·2; S, 8·1%). With water this *compound* was hydrolysed completely to colloidal iridium oxide and sulphurous and hydrofluoric acid; there was no evidence of the IrF_6^{--} ion. The compound, IrF_6,SF_4, when heated at 10^{-2} mm. melted at 125—130°, with decomposition and release of sulphur tetrafluoride, to a brown oil. But even after refluxing at 150° until no further evolution of vapour was observed, the liquid still contained much sulphur tetrafluoride (cf. the reaction between iridium hexafluoride and selenium tetrafluoride; Hepworth, Robinson, and Westland[5]).

(f) *Sulphur dioxide.* Pure liquid sulphur dioxide dissolved iridium hexafluoride to form a deep orange-red solution which, after the removal of the solvent in a vacuum at room temperature, left orange-brown crystals of a *compound* IrF_6,SO_2 (Found: Ir, 55·5; F, 26·9; SO_2, 17·1%; equiv., 355. IrF_6O_2S requires Ir, 54·8; F, 27·0; SO_2, 18·2%; equiv., 352). In water, this was hydrolysed immediately to colloidal iridium oxide, sulphur dioxide, and hydrofluoric acid, and, in a vacuum at 40°, decomposed to an unidentified gas and iridium tetrafluoride.

(g) *Nitric oxide.* This was prepared by the action of dilute nitric acid on copper, freed from nitrogen peroxide by bubbling through 10% sodium hydroxide solution, and stored over air-free water. Before use, the nitric oxide was led in a stream of oxygen-free nitrogen through traps at −75° and over phosphoric oxide to remove moisture and easily condensed impurities. Reaction between solid iridium hexafluoride and nitric oxide began at −75°, was completed by heating to 60° for 15 min., and left a pale yellow powder, *nitrosonium hexafluoroiridate*(IV) [Found: Ir, 52·5; F, 31·7; NO, 16·5. $(NO)_2IrF_6$ requires Ir, 52·6; F, 31·1; NO, 16·3%]. (There was no sign of a concurrent formation of iridium tetrafluoride or nitrosonium fluoride.) This reacted vigorously with water, evolving oxides of nitrogen and forming hexafluoroiridic(IV) acid, H_2IrF_6. The structure of the latter was proved by the precipitate of white barium hexafluoroiridate(IV) (identified by a Debye *X*-ray photograph) produced by aqueous barium nitrate. The nitrosonium salt was stable up to 250°, above which it darkened and finally melted to a black viscous liquid which could be distilled unchanged at 250—300° in a vacuum. On cooling, the liquid readily solidified to a black *product* having the composition $(NO)_2IrF_6$ [Found: Ir, 56·5; F, 27·9; NO, 17·0. $(NO)_2IrF_6$ requires Ir, 55·5; F, 27·3; NO, 17·2%]. Its reactions suggested the complex fluoride of tervalent iridium $(NO^+)_2IrF_6^{--}$. It dissolved completely in water, evolving oxides of nitrogen and forming a red solution which, when boiled, gave a precipitate of an iridium oxide. When passed through a cation-exchange resin the red material was absorbed, leaving the solution dark olive-green. Aqueous potassium hydroxide precipitated dark green iridium oxide and turned the solution green, indicating the presence of tervalent iridium (cf. Peacock[9]).

(h) *Dinitrogen tetroxide.* Dinitrogen tetroxide was condensed on to phosphoric oxide at −20° and purified by trap-to-trap distillation in a stream of dry oxygen. Liquid dinitrogen tetroxide was first tried but in it, as in sulphur trioxide, the hexafluoride proved to be insoluble; the reaction was slow, and the product obviously heterogeneous. Homogeneity was attained by

[8] Dwyer and Gyarfas, *J. Proc. Roy. Soc. New South Wales*, 1950, **84**, 123.
[9] Peacock, *J.*, 1955, 3291.

employing the vapours. Each, carried by nitrogen, was led into a 150 ml. bulb. Reaction was immediately evinced by formation of a white solid on the walls near the point of mixing. Analysis showed this to be *nitronium hexafluoroiridate*(IV) [Found: Ir, 48·4; F, 28·6. $(NO_2)_2IrF_6$ requires Ir, 48·4; F, 28·6%]. It reacted with water to form nitric acid and hexafluoroiridic(IV) acid, the latter being characterised by the precipitation of barium hexafluoroiridate(IV). When heated in a vacuum, nitronium hexafluoroiridate(IV), analogously to nitrosonium hexafluoroiridate(IV), formed a *compound* $(NO_2)_2IrF_5$ [Found: Ir, 50·1; F, 25·4. $(NO_2)_2IrF_5$ requires Ir, 50·8; F, 25·0%]. The reactions of this compound were similar to those of the corresponding nitrosonium compound, $(NO)_2IrF_6$, except that with water the nitronium fragment gave nitric acid.

Analysis.—Iridium and fluorine were determined as metal and lead chlorofluoride, respectively, by the methods described by Hepworth, Robinson, and Westland.[1]

Sulphur was determined as barium sulphate in the filtrate after removal of the iridium and oxidation of any sulphite by the addition of a few ml. of hydrogen peroxide (100-vol.), the solution being made 2N with hydrochloric acid to prevent precipitation of barium fluoride.

For determination of nitrogen, the individual compounds were decomposed in 10% aqueous sodium hydroxide and, after boiling, the solutions were filtered from iridium oxide. The nitrogen was determined in aliquot parts of the filtrate by reducing the nitrate or nitrite to ammonia with Devarda's alloy, absorbing the ammonia in 2% boric acid solution, and titrating it with 0·01N-hydrochloric acid, following the method of Kieselbach.[10]

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[10] Kieselbach, *Ind. Eng. Chem., Anal.*, 1944, **16**, 764.

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863. *The Composition of* Hakea acicularis *Gum.*

By A. M. STEPHEN.

The polysaccharide gum from *Hakea acicularis* has an acid equivalent weight of *ca.* 2000, and on hydrolysis yields L-arabinose (19%), D-xylose (8%), D-galactose (58%), D-mannose (7%), and D-glucuronic acid (8%). Its complexity resembles that of wild cherry gum and gum ghatti, and the partial hydrolysis products have not hitherto yielded a pure neutral disaccharide. Isolation of 2-*O*-β-D-glucuronosyl-D-mannose indicates that the mode of union of the mannose and acid residues is the same as in gum ghatti and in damson and cultivated cherry gums; mannose is almost certainly linked to galactose in the polysaccharide. The gum has been submitted to periodate oxidation both before and after mild acid hydrolysis.

HITHERTO the majority of plant gums studied have been collected from trees of the families *Leguminosae* and *Rosaceae*, and there is no record of work on *Proteaceae* gums. In view of the growing tendency [1-3] to relate gum composition to source of origin, it is desirable that the field of investigated types should be extended as widely as possible. The present work is a survey of the composition of the gum exudate from the bark of *Hakea acicularis*, a species introduced into South Africa from Australia during the past century. The tree grows and increases rapidly, and has spiny leaves and characteristic almond-like fruit. Gum occurs infrequently but, when it does, it may be found in very large quantity on one tree. The family (*Proteaceae*) to which *Hakea* belongs is widely distributed in the western regions of the Cape Province.

[1] Challinor, Haworth, and Hirst, *J.*, 1931, 258; Smith, *J.*, 1939, 744, 1724; Jackson and Smith, *J.*, 1940, 74, 79.
[2] Stephen, *J.*, 1951, 646; Hirst and Perlin, *J.*, 1954, 2622; Charlson, Nunn, and Stephen, *J.*, 1955, 269, 1428.
[3] Aspinall, Hirst, and Matheson, *J.*, 1956, 989.

Purified by precipitation in acidified ethanol in the usual way,[4] the gum has an equivalent weight as acid of *ca.* 2000, a value difficult to obtain with certainty owing to the low solubility of the material in water. The homogeneity of the gum is open to some doubt on account of this insolubility (which is not due, as in *Khaya grandifolia* gum,[3] to the presence of a small proportion of acetate groups). Acid hydrolysis of the gum reveals the presence of sugars corresponding in chromatographic behaviour to arabinose, xylose, mannose, and galactose, together with glucuronic acid (glucurone). Hydrolysis with 0·01N-sulphuric acid splits off a relatively low proportion (*ca.* 12% by weight) of the sugar residues present in the gum, most of the arabinose and some xylose and galactose being removed by this treatment. The residual polysaccharide, on being heated with N-sulphuric acid, liberates the remaining arabinose, together with xylose and much galactose, without the production of neutral oligosaccharides in quantity sufficient for structural examination. Mannose and glucuronic acid are split off about the same time, there remaining at this point an aldobiouronic acid (2-*O*-β-D-glucuronosyl-D-mannose), together with oligosaccharides in small amount containing this acid linked to D-galactose. The yield of aldobiouronic acid available is low on account of the low acid content of the gum and the apparent firmness of bonding of mannose to galactose. The sugars and glucuronic acid (all in their customary configurations) were identified and assayed by their isolation and the formation of suitable derivatives. Some unidentified monosaccharide material (0·3% by weight) was obtained on dilute acid hydrolysis of the gum, but this is of questionable constitutional importance.

Mannose and glucuronic acid are present in approximately equimolecular amounts in the gum, and it appears that all of the mannose is bound through $C_{(2)}$ to glucuronic acid; this is not the case in gum ghatti,[5] which *Hakea acicularis* gum resembles in the complexity of sugar residues present. Hydrolysis under comparable conditions gives no evidence for the liberation from *Hakea acicularis* gum of a glucuronosyl galactose, which is produced from gum ghatti.

Preliminary oxidation of the gum with periodate under the usual conditions resulted in uptake of the oxidant and liberation of acid per equivalent similar to that found for gum ghatti. The gum after mild acid hydrolysis consumed rather less periodate per equivalent but gave a relatively higher yield of acid, suggesting the presence of a high proportion of 1 : 6-linked galactose units in the resistant backbone of the gum molecule.

Experimental

The paper (Whatman No. 1) chromatograms were run at *ca.* 20° in butanol–ethanol–water (5 : 1 : 4, upper layer), in ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4), or in butanol–pyridine–water (9 : 2 : 2). Specific rotations were measured in water unless otherwise stated. The trees were identified through the courtesy of the Bolus herbarium.

Hakea acicularis *Gum.*—Initially soft, the exudate from the bark of *Hakea acicularis* dried to an intensely hard, horny mass, colourless unless contaminated by reddish extractives from the bark. Dispersion of the aged gum in water was almost impossible, whereas fresh soft gum dissolved completely. On storage of the hardened gum in 0·5N-hydrochloric acid for several months, partial hydrolysis with the liberation of sugars occurred, and a solution of high viscosity was obtained. Crushed nodules of gum, extracted with hot ethanol, contained no *O*-acetyl group. When purified by precipitation of an aqueous solution with ethanol in the usual way, fresh gum was converted into a colourless acidic powder, $[\alpha]_D$ −13° (*c* 0·8 in dilute alkali) (Found: equiv., *ca.* 2000; ash, <1%; I val. by Baker and Hulton's method,[6] 1·48 c.c. of 0·1N-iodine per g. of gum). Oxidation of the gum with periodate[7] for 3 days caused the liberation of 4 equivs. of acid with uptake of *ca.* 11 mols. of reagent per equiv. of gum.

Hydrolysis of the Gum.—When the gum (183 g.) was heated with 0·01N-sulphuric acid at 96° for 68 hr., there was an upward change in rotation and an increase in iodine value which fell off to a constant level; the product was then separated, by precipitation of the concentrated neutralised (barium carbonate) solution with methanol, into a mixture of sugars (19·5 g.), a degraded polysaccharide (155 g., as barium salt), and a partially soluble oligosaccharide (1·6 g., as barium salt) of $[\alpha]_D$ *ca.* +10°.

[4] Brown, Hirst, and Jones, *J.*, 1948, 1677.
[5] Aspinall, Hirst, and Wickstrøm, *J.*, 1955, 1160.
[6] Baker and Hulton, *Biochem. J.*, 1920, **14**, 754.
[7] Hirst and Jones, *J.*, 1947, 1064.

The sugar mixture was composed of L-arabinose {(15·9 g.; a portion recrystallised from methanol had m. p. and mixed m. p. 160°, $[\alpha]_D$ +102°, and yielded a phenylosazone, m. p. 164° (decomp.) (lit., m. p. 164—166°)}, D-galactose (2·1 g.; this yielded mucic acid, m. p. and mixed m. p. 219°, on oxidation), D-xylose (1·0 g.), and unidentified monosaccharides (0·5 g.) which included material similar in chromatographic behaviour and appearance on spraying to ribose and rhamnose. The weights of the individual sugars were obtained from the quantities separated from an aliquot part on a cellulose column by using aqueous butanol (water–butanol ratio, 1 : 10).

The degraded polysaccharide barium salt (Found: Ba, 3·7%), after reprecipitation through the free acid, had $[\alpha]_D$ +8°. Periodate oxidation caused liberation of 4 equivs. of acid per equivalent (1800) of gum, while 8 mols. of periodate were consumed. Further hydrolysis of the polysaccharide (81 g.) in boiling N-sulphuric acid for 10 hr. gave a mixture which, after conversion into barium salts and precipitation in ethanol in the usual way, could be divided into a sugar fraction A (61·2 g.), and a barium salt fraction B (10·4 g.) which had $[\alpha]_D^{20}$ −30° (*c* 0·34) (Found: Ba, 17·1%). Separation of the sugar fraction into its components by standard techniques yielded D-galactose {41·8 g.; m. p. 161—164° and $[\alpha]_D^{18}$ +80° (*c* 1·4) after recrystallisation from methanol–acetone; oxidation afforded mucic acid}, L-arabinose {6·5 g.; m. p. and mixed m. p. 157°, $[\alpha]_D^{20}$ +100° (*c* 0·5); derived benzoylhydrazone, m. p. and mixed m. p. 205°, and $[\alpha]_D^{20}$ +46° (*c* 0·45 in pyridine; one week in storage)}, D-xylose {5·6 g.; m. p. and mixed m. p. 150—151°, $[\alpha]_D^{20}$ +24° (*c* 1·1); derived mono-*O*-benzylidene dimethyl acetal, m. p. and mixed m. p. 212—213° and $[\alpha]_D^{20}$ −3° (*c* 1·5 in $CHCl_3$)}, and D-mannose {2·4 g.; derived phenylhydrazone, m. p. and mixed m. p. 197° (decomp.) and $[\alpha]_D^{22}$ +29° ⟶ +12° in 6 hr. (*c* 0·48 in pyridine)}.[8] In addition, elution with water after the monosaccharides had been taken off the cellulose column with water–butanol (3 : 40) afforded a mixture of oligosaccharides (5·0 g.), R_{gal} 0·63 and 0·45 in the acid solvent but with much streaking; further hydrolysis of this gave mainly galactose, with some arabinose, mannose, and a uronic acid component (paper-chromatographic identification). The weights of sugars recorded above were computed from the recovery of each sugar on elution of a portion (18·4 g.) of the original mixture from a cellulose column. Hydrolysis of the polysaccharide for 5 hr., instead of 10 hr. as described above, gave galactose, arabinose, and xylose with only a trace of mannose, together with glucuronosylmannose and two slower-moving (paper chromatogram) fractions which each yielded complicated mixtures of sugars and sugar acids on hydrolysis.

The barium salt fraction B, when chromatographed on paper with the acid solvent, was found to contain a uronic acid, an aldobiouronic acid (R_{gal} 0·5), and a trace of galactose. The de-ionised (Amberlite IR-120 H) mixture was chromatographed on cellulose, elution being with butanol–water–formic acid (45 : 4 : 1); there were obtained the following fractions: (1) Traces of sugars (xylose, arabinose, galactose), followed by D-glucuronic acid, reprecipitated as barium salt (2·3 g.), $[\alpha]_D^{22}$ +15° (*c* 1·02) (Found: Ba, 27·5%); removal of barium ion [Amberlite IR-120(H) resin] and concentration of the aqueous solution gave glucuronic acid and glucurone (paper-chromatographic identification). (2) Aldobiouronic acid, isolated as barium salt (3·7 g.), $[\alpha]_D^{22}$ −30° (*c* 0·96), R_{gal} 0·56 (acid solvent) (Found: Ba, 16·5%). (3) Residues, washed from the column with water and recovered as barium salt (3·0 g.), R_{gal} 0·6 with streaking from origin (there being indications of material concentrated at R_{gal} 0·6, 0·4, and 0·25) in acid solvent; no movement in basic solvent.

Identification of Aldobiouronic Acid.—Hydrolysis of the above-mentioned aldobiouronic acid, by 2N-sulphuric acid at 100° for 16 hr., yielded mannose, glucuronic acid, and glucurone (paper chromatograms). Methylation of the aldobiouronic acid (2·5 g.) with dimethyl sulphate–sodium hydroxide and then methyl iodide–silver oxide gave, after extraction with chloroform and removal of solvent, a syrup (1·25 g.), b. p. 180—190° (bath)/0·02 mm., $[\alpha]_D^{18}$ −25° (*c* 0·52). This was heated for 12 hr. with 1·5N-sulphuric acid at 100°, and the mixture was then neutralised with barium carbonate, centrifuged, and evaporated to near dryness under reduced pressure. Exhaustion of the concentrate with chloroform yielded a pale yellow syrup (0·18 g.), R_{MG} 0·94 (acid solvent), 0·95 (basic solvent), and 0·96 (neutral solvent), together with a faster-moving impurity, R_{MG} 1·06, 1·13, and 1·13 (R_{MG} 1·00 for tetra-*O*-methylgalactose). When sprayed with the periodate–benzidine reagent of Cifonelli and Smith [9] only the slower-moving material was detectable. The two components were separated on filter-paper sheets, yielding the slower-moving material as a syrup which crystallised after long storage in a desiccator. Recrystallisation from ether gave elongated colourless prisms, m. p. 104°, proved identical (*X*-ray powder

[8] Butler and Cretcher, *J. Amer. Chem. Soc.*, 1931, **53**, 4358.
[9] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.

diagram) with authentic 3 : 4 : 6-tri-*O*-methyl-D-mannose. The minor component, $[\alpha]_D$ +49° (*c*, 3·65 in $CHCl_3$), yielded 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid on mild alkaline hydrolysis followed by removal of cation with Amberlite IR-120(H) resin (see below). It was furthermore indistinguishable in its behaviour on paper chromatograms from the methyl ester of 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid, and in the orange colour given on spraying with *p*-anisidine hydrochloride and aniline hydrogen oxalate.

The aqueous solution of the methylated barium salt obtained as above after hydrolysis of the methylated aldobiouronic acid was treated in the usual way, to yield a syrup (0·31 g.) whose rate of movement on paper, in all three chromatographic solvents used, was the same as that of a specimen of 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid (prepared by methylation of D-glucurono-lactone). The acid was converted into its barium salt and washed with ether to remove traces of neutral material, a chromatographically pure white solid (0·23 g.), $[\alpha]_D$ +33° (*c* 2·3), being obtained. Identification of the acid was completed by conversion of this barium salt into the amide of methyl 2 : 3 : 4-tri-*O*-methyl-α-D-glucuronoside, m. p. and mixed m. p. 182° after recrystallisation from ether.

Direct paper-chromatographic comparison of the aldobiouronic acid with 2-*O*-β-D-glucuronosyl-D-mannose obtained from gum ghatti [5] showed identity of the two specimens. The homogeneity of the acid was further demonstrated by paper ionophoresis [10] in alkaline borate buffer, a single discrete spot being obtained.

Hydrolysis of Residues.—A portion of the residues (3, above) (0·5 g.) was heated on a water-bath with N-sulphuric acid (10 c.c.), samples being taken at 2, 4, and 6 hr. and chromatographed on paper. There were liberated arabinose, xylose (traces), mannose, galactose, and glucuronic acid, while the three main oligosaccharide components remained (they must obviously have diminished in quantity during hydrolysis). The total oligosaccharide fraction was separated from the sugars by precipitation as barium salt, then placed on filter-paper sheets in order to separate three fractions, R_{gal} 0·64, 0·43, and 0·28 (acid solvent) (yields : 35, 10, and 11 mg. respectively). The fastest-moving of these was chromatographically identical with the above aldobiouronic acid, and gave mannose, glucuronic acid, and glucurone on further hydrolysis. Each of the two other fractions furnished galactose as well as mannose and glucuronic acid on hydrolysis and so are not aldobiouronic acids (though they may contain traces of aldobiouronic acid).

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DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CAPE TOWN. [*Received, June 11th*, 1956.]

[10] Consden and Stanier, *Nature*, 1952, **169**, 783.

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864. 4 : 4-*Dimethylsteroids. Part II.*[1] *Some Androstane and Pregnane Derivatives.*

By (MRS.) W. J. ADAMS, D. K. PATEL, V. PETROW, (MRS.) I. A. STUART-WEBB, and B. STURGEON.

The conversion of some 3-oxo-Δ^4-derivatives of androstane and pregnane into the corresponding 4 : 4-dimethyl-3-oxo-Δ^5-derivatives and thence into the 3β-hydroxy-4 : 4-dimethyl-Δ^5-steroids is described.

4 : 4-Dimethyl-17β-propionyloxy- and 17β-hydroxy-4 : 4 : 17α-trimethyl-androsta-1 : 5-dien-3-one have been prepared from the corresponding 5-enes by procedures involving bromination at $C_{(6)}$ and dehydrobromination with lithium chloride–dimethylformamide.

WORK on 4 : 4-dimethyl-steroids is now extended to some derivatives of androstane and pregnane, which were required for biological study.

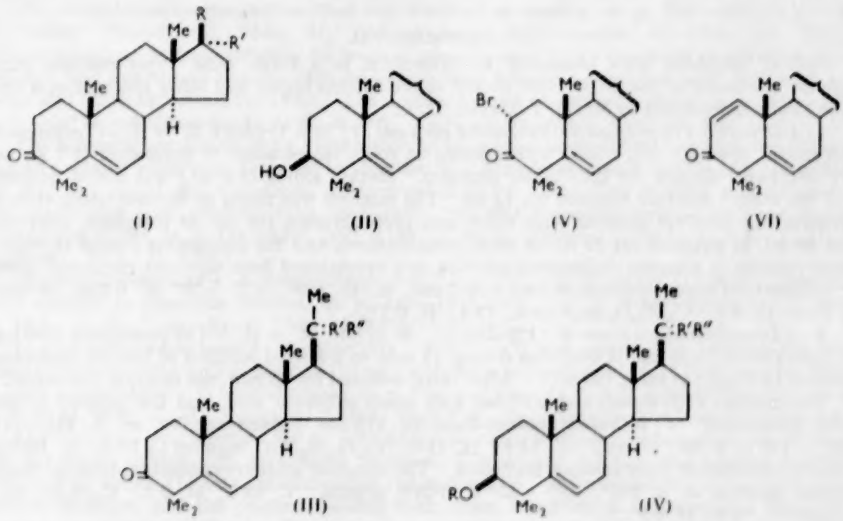
Dimethylation of testosterone propionate by the method described in Part I,[1,2]

[1] Part I, Cooley, Ellis, and Petrow, *J.*, 1955, 2998.
[2] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852.

followed by propionylation gave 4 : 4-dimethyl-17β-propionyloxyandrost-5-en-3-one (I; R = O·COEt, R′ = H), reduced by lithium aluminium hydride to 4 : 4-dimethylandrost-5-ene-3β : 17β-diol (II; R = OH, R′ = H). 17β-Acetoxy-17α-methylandrost-4-en-3-one [3] gave 17β-acetoxy-4 : 4 : 17α-trimethylandrost-5-en-3-one (I; R = OAc, R′ = Me) on dimethylation, converted into 4 : 4 : 17α-trimethylandrost-5-ene-3β : 17β-diol (II; R = OH, R′ = Me) by lithium aluminium hydride. 17β-Acetoxy-17α-ethynylandrost-4-en-3-one [4] similarly furnished 17β-acetoxy-17α-ethynyl-4 : 4-dimethylandrost-5-en-3-one (I; R = OAc, R′ = C:CH) and 17α-ethynyl-4 : 4-dimethylandrost-5-ene-3β : 17β-diol (II; R = OH, R′ = C:CH). 17β-Acetoxy-17α-vinylandrost-4-en-3-one [5] gave 17β-acetoxy-4 : 4-dimethyl-17α-vinylandrost-5-en-3-one (I; R = OAc, R′ = CH:CH_2).

Extension of the dimethylation procedure to 17-oxoandrostane and 20-oxopregnane derivatives in general required protection of these oxo-groups, for which purpose the ethylenedioxy-derivatives proved suitable.

3β-Hydroxyandrost-5-en-17-one was converted into 17 : 17-ethylenedioxyandrost-5-en-3β-ol,[6] which passed into 17 : 17-ethylenedioxyandrost-4-en-3-one on Oppenauer oxidation. This method of preparation of the last compound is preferred to the direct monoketalisation of androstenedione.[7] Dimethylation of 17 : 17-ethylenedioxyandrost-4-en-3-one furnished 17 : 17-ethylenedioxy-4 : 4-dimethylandrost-5-en-3-one, reduced to 17 : 17-ethylenedioxy-4 : 4-dimethylandrost-5-en-3β-ol, which was converted into 3β-hydroxy-4 : 4-dimethylandrost-5-en-17-one on treatment with acid. Pregnenolone was



The partial formula omitted from (II), (V), and (VI) is as in (I).

converted into 20 : 20-ethylenedioxypregn-5-en-3β-ol and thence into 20 : 20-ethylenedioxypregn-4-en-3-one. Dimethylation gave 20 : 20-ethylenedioxy-4 : 4-dimethylpregn-5-en-3-one (III; R′R″ = O·CH_2·CH_2·O) which passed into 3β-hydroxy-4 : 4-dimethylpregn-5-en-20-one (IV; R = H, R′R″ = O) on reduction and hydrolysis. Surprisingly, direct dimethylation of progesterone gave the dimethyl derivative (III; R′R″ = O) in *ca.*

[3] Miescher and Klarer, *Helv. Chim. Acta*, 1939, **22**, 962.
[4] Ruzicka and Meldahl, *ibid.*, 1938, **21**, 1760.
[5] Ruzicka, U.S.P. 2,272,131/1942.
[6] Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.
[7] Herzog, Jevnik, Tully, and Hershberg, *ibid.*, 1953, **75**, 4425.

45% yield. This result contrasts with the oxalylation of progesterone which yields only the 21-oxalyl derivative.[8,9]

Monobromination of 4 : 4-dimethylcholest-5-en-3-one furnished 2α-bromo-4 : 4-dimethylcholest-5-en-3-one (V; R = C_8H_{17}, R′ = H),[10] no evidence for 5 : 6-addition being obtained. The compound failed to form a dinitrophenylhydrazone and was not dehydrobrominated in this reaction. Treatment with collidine gave 4 : 4-dimethylcholest-5-en-3-one and a small quantity of the required 4 : 4-dimethylcholesta-1 : 5-dien-3-one (VI; R = C_8H_{17}, R′ = H), which was readily obtained, however, by the use of lithium chloride in dimethylformamide for the dehydrobromination.[11] The dienone (VI; R = C_8H_{17}, R′ = H) was additionally obtained, albeit in very low yield, by direct dimethylation of cholesta-1 : 4-dien-3-one. An attempt to enforce the molecular rearrangement of the dienone (VI; R = C_8H_{17}, R′ = H) with sulphuric acid–acetic anhydride proved unsuccessful. Dibromination of 4 : 4-dimethylcholest-5-en-3-one gave the dibromo-derivative (see Experimental section). Bromination of 17β-acetoxy-4 : 4 : 17α-trimethylandrost-5-en-3-one (I; R = OAc, R′ = Me) followed by dehydrobromination of the product, gave 17β-acetoxy-4 : 4 : 17α-trimethylandrosta-1 : 5-dien-3-one (VI; R = OAc, R′ = Me), which was converted into 17β-hydroxy-4 : 4 : 17α-trimethylandrosta-1 : 5-dien-3-one (VI; R = OH, R′ = Me) by lithium aluminium hydride reduction followed by oxidation with chromic acid–pyridine. 4 : 4-Dimethyl-17β-propionyloxyandrosta-1 : 5-dien-3-one (VI; R = O·COEt, R′ = H) was prepared similarly from 4 : 4-dimethyl-17β-propionyloxyandrost-5-en-3-one (I; R = O·COEt, R′ = H).

Experimental

Optical rotations were measured in chloroform in a 1-dm. tube. Spectroscopic transparency in ethanol of the methylated steroid in the 240-mμ region and other spectroscopic data were kindly determined by Mr. M. T. Davies, B.Sc.

4 : 4-*Dimethyl*-17β-*propionyloxyandrost*-5-*en*-3-*one* (I; R = O·COEt, R′ = H).—Testosterone propionate (4·96 g.) was added with stirring at room temperature to potassium (1·7 g.) and dry *tert.*-butyl alcohol (50 ml.) under nitrogen. Methyl iodide (5·5 ml.) was added dropwise and the stirred mixture refluxed for 1½ hr. The mixture was taken to dryness under reduced pressure, the product isolated with ether and propionylated (20 ml. of propionic anhydride and 20 ml. of pyridine for 16 hr. at room temperature), and the propionate passed through a short column of alumina in benzene solution and crystallised from aqueous methanol, giving 4 : 4-*dimethyl*-17β-*propionyloxyandrost*-5-*en*-3-*one*, m. p. 120°, $[\alpha]_D^{27}$ −29° (*c*, 0·376) (Found : C, 77·5; H, 9·5. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

4 : 4-*Dimethylandrost*-5-*ene*-3β : 17β-*diol* (II; R = OH, R′ = H).—The propionate (300 mg.) in ether (30 ml.) was added dropwise during 15 min. to a stirred solution of lithium aluminium hydride (300 mg.) in ether (30 ml.). After being refluxed for 30 min. the mixture was cooled to 0°, decomposed with water, and acidified with dilute sulphuric acid, and the product isolated with chloroform. 4 : 4-*Dimethylandrost*-5-*ene*-3β : 17β-*diol* formed needles, m. p. 210—211°, $[\alpha]_D^{23}$ −79° (*c*, 0·207) (Found : C, 75·8; H, 11·0. $C_{21}H_{34}O_2,H_2O$ requires C, 75·0; H, 10·7%), after crystallisation from aqueous methanol. The *diacetate*, after crystallisation from methanol, formed needles, m. p. 170°, $[\alpha]_D^{25}$ −83° (*c*, 0·210) (Found : C, 73·3; H, 9·1. $C_{25}H_{38}O_4,\frac{1}{2}H_2O$ requires C, 73·0; H, 9·5%).

17β-*Acetoxy*-4 : 4 : 17α-*trimethylandrost*-5-*en*-3-*one* (I; R = OAc, R′ = Me) formed plates, m. p. 162—163°, $[\alpha]_D^{23}$ −21° (*c*, 0·297) (Found : C, 77·3; H, 9·8. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

4 : 4 : 17α-*Trimethylandrost*-5-*ene*-3β : 17β-*diol* (II; R = OH, R′ = Me) crystallised from aqueous methanol, yielding needles, m. p. 218°, $[\alpha]_D^{26}$ −118° (*c*, 0·243) (Found : C, 79·3; H, 11·0. $C_{22}H_{36}O_2$ requires C, 79·5; H, 10·8%). The 3-monoacetate had m. p. 149°, $[\alpha]_D^{23}$ −89° (*c*, 0·248). The *diacetate*, prepared by refluxing the diol for 6 hr. with acetic anhydride–pyridine, separated from aqueous methanol in fine needles, m. p. 164°, $[\alpha]_D^{26}$ −71° (*c*, 0·284) (Found : C, 75·1; H, 9·8. $C_{26}H_{40}O_4$ requires C, 75·0; H, 9·6%).

[8] Upjohn Company, B.P. 738,445/1955.

[9] Cf. Hogg, Beal, Nathan, Lincoln, Schneider, Magerlein, Hanze, and Jackson, *J. Amer. Chem. Soc.*, 1955, **77**, 4436.

[10] See Corey, *ibid.*, 1953, **75**, 4832; 1954, **76**, 175, for configuration of 2-bromo-compounds.

[11] Cf. Holysz, *ibid.*, 1953, **75**, 4432.

17β-*Acetoxy*-17α-*ethynyl*-4 : 4-*dimethylandrost*-5-*en*-3-*one* (I; R = OAc, R′ = C:CH) formed plates, m. p. 199—200°, $[\alpha]_D^{24}$ −67° (*c*, 0·410) (Found : C, 78·3; H, 8·6. $C_{23}H_{34}O_2$ requires C, 78·5; H, 8·9%), after crystallisation from acetone–hexane. The infrared absorption spectrum, kindly determined by Dr. A. E. Kellie, showed the presence of an acetylenic hydrogen atom, showing that methylation at the acetylenic centre had not occurred.

17α-*Ethynyl*-4 : 4-*dimethylandrost*-5-*ene*-3β : 17β-*diol* (II; R = OH, R′ = C:CH) separated from acetone–hexane in micro-crystals, m. p. 222—224°, $[\alpha]_D^{23}$ −133° (*c*, 0·29) (Found : C, 80·5; H, 9·4. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·9%).

17β-*Acetoxy*-4 : 4-*dimethyl*-17α-*vinylandrost*-5-*en*-3-*one* (I; R = OAc, R′ = CH:CH_2) formed prisms, m. p. 191—192°, $[\alpha]_D^{22}$ +19° (*c*, 0·313) (Found : C, 78·6; H, 9·4. $C_{23}H_{34}O_2$ requires C, 78·1; H, 9·4%), after crystallisation from acetone–hexane.

17 : 17-Ethylenedioxyandrost-4-en-3-one was prepared by Oppenauer oxidation of 17 : 17-ethylenedioxyandrost-5-en-3β-ol with aluminium *tert.*-butoxide in toluene–*cyclo*hexanone.

17 : 17-*Ethylenedioxy*-4 : 4-*dimethylandrost*-5-*en*-3-*one* formed prisms, m. p. 128—129°, $[\alpha]_D^{27}$ −40° (*c*, 0·741) (Found : C, 77·0; H, 9·7. $C_{23}H_{34}O_2$ requires C, 77·1; H, 9·5%), after crystallisation from acetone–hexane.

17 : 17-*Ethylenedioxy*-4 : 4-*dimethylandrost*-5-*en*-3β-*ol* was purified from methanol, yielding needles, m. p. 214°, $[\alpha]_D^{25}$ −109° (*c*, 0·355) (Found : C, 76·7; H, 9·7. $C_{23}H_{36}O_2$ requires C, 76·7; H, 10·0%).

3β-*Hydroxy*-4 : 4-*dimethylandrost*-5-*en*-17-*one* was prepared by refluxing the ethylenedioxy-compound (2·08 g.) in ethanol (110 ml.) with dilute sulphuric acid (15 ml. of 8·5% v/v) for 1 hr.; it formed needles, m. p. 190—191°, $[\alpha]_D^{27}$ +35° (*c*, 0·29) (Found : C, 79·2; H, 10·1. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·1%), after crystallisation from aqueous methanol.

20 : 20-*Ethylenedioxypregn*-5-*en*-3β-*ol* was obtained as needles, m. p. 160—161°, $[\alpha]_D^{26}$ −45° (*c*, 0·396) (Found : C, 73·0; H, 10·1. $C_{23}H_{36}O_3.H_2O$ requires C, 73·0; H, 10·1%) after crystallisation from ethanol, by heating pregnenolone (5 g.) dissolved in ethylene glycol (50 ml.) and anhydrous benzene (150 ml.) containing toluene-*p*-sulphonic acid (150 mg.) in a Dean and Stark apparatus for 16 hr. The acetate formed shimmering plates, m. p. 159—160°, $[\alpha]_D^{25}$ −54° (*c*, 0·4) (Found : C, 74·6; H, 9·5. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

The foregoing compound (2·8 g.) was dissolved in *cyclo*hexanone (18 ml.) and toluene (20 ml.), and all traces of water were removed by distillation. Aluminium *tert.*-butoxide (4 g.) in toluene (10 ml.) was added and the stirred mixture refluxed for 3 hr. The product was isolated in the usual way and purified from methanol. 20 : 20-*Ethylenedioxypregn*-4-*en*-3-*one* formed shimmering plates, m. p. 188—190°, $[\alpha]_D^{26}$ +101° (*c*, 0·458) (Found : C, 76·8; H, 9·5. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·5%).

20 : 20-*Ethylenedioxy*-4 : 4-*dimethylpregn*-5-*en*-3-*one* (III; R′R″ = O·CH_2CH_2·O) separated from acetone in prismatic needles, m. p. 189—191°, $[\alpha]_D^{24}$ −8° (*c*, 0·404) (Found : C, 77·7; H, 10·0. $C_{25}H_{38}O_3$ requires C, 77·3; H, 9·9%).

4 : 4-*Dimethylpregn*-5-*ene*-3 : 20-*dione* (III; R′R″ = O) was prepared by treating the foregoing compound (100 mg.) in acetone (10 ml.) with toluene-*p*-sulphonic acid (100 mg.) for 16 hr. at room temperature. It formed prisms, m. p. 128° and 140—141°, $[\alpha]_D^{24}$ +64° (*c*, 0·466) (Found : C, 80·6; H, 10·2. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·9%), after crystallisation from ether–pentane.

Alternatively, progesterone (10 g.) was added at room temperature to potassium (3·73 g.) and *tert.*-butyl alcohol (100 ml.) under nitrogen. The stirred mixture was treated dropwise with methyl iodide (14 ml.), heated under reflux for 1 hr., and evaporated to dryness under reduced pressure, and the product isolated with ether, dissolved in benzene, and chromatographed on alumina (200 g.). The benzene–light petroleum (b. p. 60—80°) eluates yielded 4 : 4-*dimethylpregn*-5-*ene*-3 : 20-*dione*, m. p. 141—142°, $[\alpha]_D^{26}$ +58° (*c*, 0·422) (Found : C, 80·7; H, 10·1%); the m. p. was not depressed on admixture with a sample prepared by the indirect route.

When the foregoing compound (4·6 g.) was heated with toluene-*p*-sulphonic acid (150 mg.) in benzene (700 ml.) and ethylene glycol (75 ml.) under reflux in a Dean and Stark apparatus for 16 hr., 20 : 20-ethylenedioxy-4 : 4-dimethylpregn-5-en-3-one was obtained; it formed prismatic needles, m. p. 190—193°, $[\alpha]_D^{25}$ −6° (*c*, 1·035) (Found : C, 77·9; H, 9·5. Calc. for $C_{25}H_{38}O_3$: C, 77·3; H, 9·9%), the m. p. not being depressed on admixture with a sample prepared as above.

Reduction of the ketal (640 mg.) in tetrahydrofuran (20 ml.) with lithium aluminium hydride (400 mg.) in tetrahydrofuran (50 ml.), followed by acetylation of the product, yielded 3β-acetoxy-20 : 20-ethylenedioxy-4 : 4-dimethylpregn-5-ene (IV; R = Ac, R′R″ = O·CH_2·CH_2·O), m. p. 171—173°, $[\alpha]_D^{24}$ −50° (*c*, 0·39).

3β-*Acetoxy*-4 : 4-*dimethylpregn*-5-*en*-20-*one* (IV; R = Ac, R′R″ = O) was prepared by treating the ethylenedioxy-compound (180 mg.) in acetone (20 ml.) with toluene-*p*-sulphonic

acid (150 mg.) for 16 hr. at room temperature, and formed plates, m. p. 178—180°, $[\alpha]_D^{25}$ +4° (*c*, 0·356) (Found : C, 77·8; H, 9·9. $C_{33}H_{38}O_3$ requires C, 77·7; H, 9·8%), from methanol.

3β-*Hydroxy*-**4** : **4**-*dimethylpregn*-5-*en*-20-*one*, leaflets, m. p. 199—202° (Found : C, 79·9; H, 10·5. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·3%), from acetone, was prepared by heating under reflux the acetate (570 mg.) in methanol (45 ml.) with potassium carbonate (500 mg.) in water (5 ml.) for 1 hr.

2α-*Bromo*-**4** : **4**-*dimethylcholest*-5-*en*-3-*one* (V; R = C_8H_{17}, R′ = H).—To a stirred solution of **4** : 4-dimethylcholest-5-en-3-one (10·2 g.) in dry ether (750 ml.), bromine (4·2 g.) in acetic acid (29 ml.) was added during 5 min. After 30 min. the mixture was poured into water, and the product isolated with ether and purified from ethanol. 2α-*Bromo*-**4** : **4**-*dimethylcholest*-5-*en*-3-*one* formed plates, m. p. 136—137°, $[\alpha]_D^{27}$ −35° (*c*, 1·1) (Found : C, 70·9; H, 9·4; Br, 16·4. $C_{29}H_{47}OBr$ requires C, 70·9; H, 9·6; Br, 16·3%). The starting material was regenerated on reduction of the bromo-compound with zinc dust and acetic acid–ether at room temperature.

This monobromo-derivative (4·1 g.) in warm acetic acid (150 ml.) was treated with bromine (1·6 g.) in acetic acid (10 ml.). After being set aside overnight the mixture was evaporated to turbidity, which was cleared with ether; it slowly gave a product (1·6 g.) which was cautiously recrystallised from ethanol with the minimum of heating to yield a *dibromo-derivative*, m. p. 94—96° (Found : C, 61·7; H, 8·3; Br, 25·5. $C_{29}H_{46}OBr_2$ requires C, 61·1; H, 8·1; Br, 28·1%). Debromination of a portion with collidine, followed by chromatography, gave a fraction having $\lambda_{max.}$ 254 mμ, a value consistent with a 2-bromo-3-oxo-Δ^1-steroid.

4 : 4-*Dimethylcholesta*-1 : 5-*dien*-3-*one* (VI; R = C_8H_{17}, R′ = H).—(*a*) The monobromo-ketone (10 g.), lithium chloride (10 g.; anhydrous), and dimethylformamide (150 ml.) were heated under reflux for 5 hr. The product was isolated with ether and purified from ethanol. **4** : 4-*Dimethylcholesta*-1 : 5-*dien*-3-*one* formed needles, m. p. 77—78°, $[\alpha]_D^{23}$ +53° (*c*, 1·00), $\lambda_{max.}$ 227 mμ (log ε 3·98) (Found : C, 84·7; H, 11·2. $C_{29}H_{46}O$ requires C, 84·9; H, 11·2%). (*b*) The monobromo-compound (5 g.) and collidine (50 ml.) were heated under reflux in nitrogen for 5 hr. After removal of collidine hydrobromide, the product was isolated with ether and purified from methanol to give **4** : 4-dimethylcholest-5-en-3-one, m. p. 169—170° not depressed on admixture with an authentic specimen. The mother liquors were taken to dryness and chromatographed in light petroleum (b. p. 60—80°) on alumina (40 g.). Elution with light petroleum (b. p. 60—80°) gave **4** : 4-dimethylcholesta-1 : 5-dien-3-one (500 mg.), m. p. 75—76°, $[\alpha]_D^{24}$ +48° (*c*, 1·14), $\lambda_{max.}$ 227 mμ (log ε 3·97). The m. p. was not depressed on admixture with an authentic sample. (*c*) A cold solution from potassium (2·4 g.) and *tert.*-butyl alcohol (125 ml.) was treated with cholesta-1 : 4-dien-3-one (7·5 g.). Methyl iodide (7·5 ml.) was added dropwise during 30 min. and the mixture then heated under reflux for 2 hr. The product, in light petroleum (b. p. 60—80°), was chromatographed on alumina (150 g.). The materials eluted by light petroleum (1000 ml.; b. p. 60—80°) and benzene–light petroleum (250 ml. of 1 : 9 v/v) were combined and similarly chromatographed on alumina (15 g.). Elution with light petroleum (2000 ml.; b. p. 60—80°) followed by crystallisation from ethanol, gave **4** : 4-dimethylcholesta-1 : 5-dien-3-one (150 mg.), m. p. and mixed m. p. 76—77°, $[\alpha]_D^{25}$ +48° (*c*, 1·1), $\lambda_{max.}$ 227 mμ (log ε 3·98).

17β-*Acetoxy*-**4** : **4** : 17α-*trimethylandrosta*-1 : 5-*dien*-3-*one* (VI; R = OAc, R′ = Me).—17β-Acetoxy-**4** : **4** : 17α-trimethylandrost-5-en-3-one (2·55 g.) in ether (150 ml.) was treated with bromine in acetic acid (0·155 g./ml.; 7·5 ml.) to give a crude 2-bromo-derivative (2·7 g.) (V; R = OAc, R′ = Me), m. p. 136—138° after crystallisation from methanol. Dehydrobromination with lithium chloride (6·0 g.) in dimethylformamide (100 ml.) gave 17β-*acetoxy*-**4** : **4** : 17α-*trimethylandrosta*-1 : 5-*dien*-3-*one*, as prisms, m. p. 168—170°, $[\alpha]_D^{24}$ +35° (*c*, 1·36), $\lambda_{max.}$ 227 mμ (log ε 3·99) (Found : C, 78·0; H, 9·3. $C_{24}H_{34}O_2$ requires C, 77·8; H, 9·2%).

17β-*Hydroxy*-**4** : **4** : 17α-*trimethylandrosta*-1 : 5-*dien*-3-*one*.—The acetate (700 mg.) in ether (20 ml.) was reduced with lithium aluminium hydride (1 g.) in ether. The crude dry product was oxidised for 16 hr. at room temperature with chromic acid (1 g.) in pyridine (20 ml.). The product was extracted with hot benzene, the extract filtered through " Hyflo," and the benzene filtrate then washed with dilute hydrochloric acid and water, and dried. The product in 50% benzene–light petroleum was trickled through a short column of alumina and then purified from acetone–hexane. 17β-*Hydroxy*-**4** : **4** : 17α-*trimethylandrosta*-1 : 5-*dien*-3-*one* formed silky needles, m. p. 168—169°, $[\alpha]_D^{26}$ +24° (*c*, 1·04), $\lambda_{max.}$ 226—227 mμ (log ε 3·97) (Found : C, 80·3; H, 9·7. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

4 : 4-*Dimethyl*-17β-*propionyloxyandrosta*-1 : 5-*dien*-3-*one* (VI; R = O·COEt, R′ = H) formed prisms, m. p. 125°, $[\alpha]_D^{22}$ +50° (*c*, 0·11), $\lambda_{max.}$ 227 mμ (log ε 4·0) (Found : C, 77·3; H, 9·0. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·2%).

7ξ-*Methoxy*-**4** : **4**-*dimethylcholest*-**5**-*en*-**3**-*one*.[12]—A suspension of **4** : 4-dimethylcholest-5-en-3-one (4·1 g.) and *N*-bromosuccinimide (2 g.) in dry carbon tetrachloride (50 ml.) was treated with benzoyl peroxide (*ca.* 20 mg.) in carbon tetrachloride. The mixture was heated under reflux for 1 hr., the succinimide removed, the filtrate evaporated to small bulk, and methanol added with warming until crystallisation commenced. 7ξ-*Methoxy*-**4** : **4**-*dimethylcholest*-**5**-*en*-**3**-*one* formed long silky needles, m. p. 155—156°, $[\alpha]_D^{26}$ +80° (*c*, 1·06) (Found : C, 81·4; H, 11·7. $C_{30}H_{50}O_2$ requires C, 81·5; H, 11·3%), after purification from ethanol. 7ξ-*Ethoxy*-**4** : **4**-*dimethylcholest*-**5**-*en*-**3**-*one* was obtained by boiling the crude bromination product with ethanol and formed prismatic needles, m. p. 129—130°, $[\alpha]_D^{26}$ +77° (*c*, 0·83) (Found : C, 81·1; H, 11·3. $C_{31}H_{52}O_2$ requires C, 81·5; H, 11·4%), from light petroleum (b. p. 40—60°).

4 : **4**-*Dimethylcholesta*-**5** : **7**-*dien*-**3**-*one*.—**4** : 4-Dimethylcholest-5-en-3-one (6·2 g.) was brominated with *N*-bromosuccinimide (3 g.) in carbon tetrachloride. Succinimide was filtered off, collidine (40 ml.) added to the filtrate, and the carbon tetrachloride evaporated off. The solution was heated in nitrogen under reflux for ½ hr. The product was isolated with ether and purified by chromatography to give **4** : **4**-*dimethylcholesta*-**5** : **7**-*dien*-**3**-*one* as plates, m. p. 160°, $[\alpha]_D^{24}$ −20° (*c*, 1·27), $\lambda_{max.}$ 274 (log ε 4·00), 283 mμ (log ε 4·02), $\lambda_{infl.}$ 295 mμ (Found : C, 85·1; H, 11·4. $C_{29}H_{46}O$ requires C, 84·9; H, 11·2%), after crystallisation from propan-2-ol.

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Chemical Research Laboratories,
The British Drug Houses, Ltd., London, N.1. [*Received, June 14th*, 1956.]

[12] Cf. Greenhalgh, Henbest, and Jones, *J.*, 1952, 2380, for $C_{(7)}$-bromination of a 5-ene followed by replacement of the bromine atom by an alkoxyl group.

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865. *Infrared Spectra of Metal Ammines and Related Compounds. Part II.* The* trans-*Effect in Platinous Complexes.*

By D. B. Powell.

Infrared spectra of a number of platinous ammine complexes in the potassium bromide region show the effect of the *trans*-directive ligands Cl, Et_2S, and C_2H_4 on the frequencies of the νPt–N vibration. The value of this frequency is directly related to the strength of bonding of the NH_3 group, and the results indicate that whereas *trans*-Cl has little effect on the strength of the Pt–N bond, diethyl sulphide and ethylene cause an appreciable bond weakening. The possible significance of this factor in consideration of the *trans*-effect is discussed.

On the basis of substitution reactions in metal complexes it is possible to arrange ligands in a series of increasing *trans*-effect, though in some cases the exact order may be doubtful. Russian authors quoted by Chatt, Duncanson, and Venanzi [1] give the following order : $H_2O < OH < NH_3 < R{\cdot}NH_2 <$ pyridine $< Cl < Br < CNS \sim I \sim NO_2 \sim SO_3H \sim PR_3 \sim R_2S \sim SC(NH_2)_2 < NO \sim CO \sim C_2H_4 \sim CN$.

Examples of the *trans*-effect have been reviewed by Quagliano and Schubert,[2] and more recently Chatt *et al.*[1] have discussed the cause of the effect. They consider that bond weakening of the *trans*-group, favouring dissociation of the complex, which had generally been assumed to be responsible, was not an important factor. It is suggested that the more strongly *trans*-directive ligands are able to form a π bond with the metal in addition to the normal σ bond; this will withdraw electrons from the metal orbitals and favour substitution in the *trans*-position through an S_N2 mechanism.

This view of the mechanism of the substitution in platinum complexes is supported by studies of the rate of exchange of Cl, Br, I, or CN in platinum complexes of the type K_2PtX_4.

* The paper by Powell and Sheppard, *J.*, 1956, 3108 is regarded as Part I.

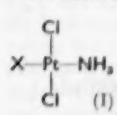
[1] Chatt, Duncanson, and Venanzi, *J.*, 1955, 4456.
[2] Quagliano and Schubert, *Chem. Revs.*, 1952, **50**, 201.

where it is found that the more rapid exchange takes place with the more stable complex; this would not be expected if the substitution took place through a dissociative type of mechanism.[3]

Chatt, Duncanson, and Venanzi [4] give spectroscopic data on the infrared N–H stretching frequencies of several amines when *trans* to groups of varying *trans*-directive strength in platinum complexes. Their results show that the apparent weakening of the Pt–N bond, as indicated by changes in the spectra due to the N–H stretching vibrations, does not follow the same order as the *trans*-directive strengths of the ligands. It is therefore concluded that bond weakening is not the main factor in determining the directive properties of a ligand.

The study of N–H vibrations can only give indirect evidence as to the nature of the M–N bond, and no estimate can be made on this basis of the numerical values of bond-strength differences. The identification of the M–N skeletal frequencies for a number of different metal ammines [5] affords a means of obtaining a more direct comparison of bond strength when an NH_3 group is *trans* to various ligands. NH_3 is a useful group on which to examine the directive effect of other groups as it is itself unlikely to show an appreciable tendency to form a double bond with the metal ion.

As a first approach to the problem, the infrared spectra of *cis*- and *trans*-isomers of $Pt(NH_3)_2Cl_2$ have been compared, as in the *cis*-compound each NH_3 is *trans* to Cl, whereas in the *trans*-compound each NH_3 is *cis* to Cl. Examination of the results showed that there is difficulty in the interpretation of the νM–N frequencies observed, since two infrared-active frequencies would be expected for the *cis*-compound, but only one for the *trans* [in practice only one frequency was detected for *cis*-$Pt(NH_3)_2Cl_2$, though both frequencies were found for the corresponding palladium compound [6]]. A group of compounds where this difficulty does not arise, and in which the *trans*-effect can be examined directly, are those of the type (I), where only one infrared-active skeletal stretching frequency would be expected. From a chemical point of view *trans*-$Pt(NH_3)_2Cl_2$ is the first member of this series and, in addition, the compounds containing Et_2S and C_2H_4 in position X have now been examined.



(I)

Spectra have been obtained in the potassium bromide region for all these compounds, together with similar compounds not containing an NH_3 group to confirm the identification of the Pt–N frequency. Spectra in the rock-salt region have also been obtained in a number of cases, either to confirm the purity of particular isomers or where the low-frequency spectra show features of particular interest. The frequencies observed are contained in the Table.

The similarity of the νM–N frequencies observed for *cis*- and *trans*-$Pt(NH_3)_2Cl_2$ as reported previously [6] indicates that Cl has no appreciable bond-weakening effect on the Pt–N bond, but it is observed that where diethyl sulphide and ethylene are ligands, they cause a significant weakening of the Pt–N bond *trans* to them, since the skeletal frequencies found (493 cm.$^{-1}$ for diethyl sulphide and 481 cm.$^{-1}$ for ethylene) are considerably smaller than those for *trans*-$Pt(NH_3)_2Cl_2$ (507 cm.$^{-1}$) or $[Pt(NH_3)_4]Cl_2$ (511 cm.$^{-1}$).[5] In view of the great mass of the platinum atom, it is very probable that the stretching frequency of the Pt–N bond does not interact with other vibrations of the rest of the molecule. We shall assume that the νPt–N vibration of the Pt–NH_3 system can be treated as that of an effectively diatomic molecule. In such a case the frequency ν is related to the force constant, k, by the relation $\nu = [k(1/M_1 + 1/M_2)]^{\frac{1}{2}}/2\pi$. It follows that, if ν_1 and ν_2 are the vibration frequencies of the same group in two different complexes, $k_1/k_2 = \nu_1^2/\nu_2^2$. Inserting the values quoted above for the νPt–N frequency in *trans*-$Pt(NH_3)_2Cl_2$ and *trans*-$Pt(NH_3)(C_2H_4)Cl_2$, we find that the force constant in the latter is 10% less than in the former.

The order of the bond weakening for the groups examined is the same as that reported by Chatt, Duncanson, and Venanzi,[4] based on the N–H stretching frequencies, but the extent of the weakening is greater than might have been expected on those results: for

[3] Grinberg and Nikol'skaya, *Zhur. prihlad. Khim.*, 1951, **24**, 893, reported in *Ann. Reports*, 1953, **50**, 49.
[4] Chatt, Duncanson, and Venanzi, *J.*, 1955, 4461.
[5] Powell and Sheppard, *J.*, 1956, 3108.
[6] Powell, *Chem. and Ind.*, 1956, 314.

the effect of various *trans*-groups on the N–H stretching frequencies of the compounds *trans*-[Pt L, piperidine, Cl_2] in dilute solution, Chatt gives the following values: L = piperidine, 3222 cm.$^{-1}$; L = Et_2S, 3223 cm.$^{-1}$; L = C_2H_4, 3230 cm.$^{-1}$. For indications of bond strength based on band intensity, the effect appears rather greater, and for the same complexes the values of 10^7B are given as 1·68, 1·66, 1·59, respectively. Several factors

Main infrared absorption frequencies of platinum complexes * (cm.$^{-1}$).

trans-$Pt(NH_3)_2Cl_2$ †	*cis*-$Pt(NH_3)_2Cl_2$	*cis*-$Pt(NH_3)_2(NO_2)Cl$	*cis*-$Pt(NH_3)_2(NO_2)_2$
507 ‡ w.	508 ‡ w.	*ca.* 510 ‡ v.w.	—
828 m.	805 m.	533 s.	No ν Pt–N frequency detected due to very strong NO_2 absorption.
1288 s. (1305)	1300 s.	545 s.	
	1317 s.		
1538 w.	1536 w.		
1638 w.	1630 w.	Not examined in rock salt region.	
3170 m.	3270 m. (3200)		
3270 m.	—		

trans-$(Et_2S)_2PtCl_2$	*cis*-$(Et_2S)_2PtCl_2$	*trans*-$(Et_2S)(NH_3)PtCl_2$	$K[Pt(C_2H_4)Cl_3]H_2O$	*trans*-$(C_2H_4)(NH_3)PtCl_2$
—	—	493 ‡ w.	500 } v.s. broad	481 ‡ w.
677 m.	677 m.	679 m.	550 } (H_2O)	
726 w.	725 w.	727 w.	620 w.	617 w.
		789 s.	717 m.	735 m.
		835 w.	—	820 w.
		975 m.	1011 s.	1010 s. (1023)
Not examined in rock-salt region.		1037 w.	1023 s.	—
		1045 w.	1240 w.	1255 s.
		1245 w.	—	1267 s.
		1284 s.	1245 s.	1422 m.
		1317 w.	1612 s.	1610 m.
		1631 m.	3480 m.	3300 s.
		3170 w.	3540 m.	—
		3260 w.	—	—

* These spectra were determined on Nujol mulls of unknown concentration, and so band strengths are only comparative for a particular spectrum. Weaker bands have been omitted except below 600 cm.$^{-1}$

† These frequencies have been recorded previously.[5]

‡ Due to νPt–N vibration.

may account for the lack of exact correlation between these methods of assessing M–N bond strengths, the most obvious being that the first ligand of the series in the present work is NH_3, whereas Chatt *et al.* used piperidine. In addition there are effects which may modify the actual vibration frequencies measured: hydrogen bonding of the ammines in the solid state may indirectly affect the νM–N value, but it is probable that changes in frequency due to this cause are very small. This effect was avoided in the νN–H values given by Chatt *et al.*[4] by the use of dilute carbon tetrachloride solutions. It has also been observed by Chatt and his co-workers that there is an interaction of the proton of the N–H bond with a *d* orbital of the platinum and that this will affect the absorption band due to the N–H vibration.

cis-$Pt(NH_3)_2Cl(NO_2)$ gave apparently a very weak absorption band at *ca.* 510 cm.$^{-1}$, but no detectable lower-frequency absorption. This seems to indicate that the nitro-group, like Cl, exerts no bond-weakening effect, though the band is too weak to allow a definite conclusion to be reached.

It would be useful to obtain some quantitative measure of the effect in terms of the stability constants of the ammines. It is appreciated that stability constants are not directly related to the bond strengths as indicated by vibration frequencies, but previous work [5] has shown that, though there is not an exact correlation, the vibration frequencies and the logarithms of the stability constants show a similar trend.

Unfortunately, there are insufficient data, on both stability constants and infrared-active skeletal vibrations of the less stable ammines, since these are expected to lie mainly below 420 cm.$^{-1}$. However, if Raman frequencies are used, some rough idea of the size of the

effect can be obtained; thus, for $[Pt(NH_3)_4]^{2+}$ no stability figures are available, but it is generally regarded as being slightly more stable than $[Co(NH_3)_6]^{3+}$, for which log $k_{average}$ is 5·9. This is supported by the νM–N frequency of 511 cm.$^{-1}$ as compared with 501 cm.$^{-1}$ found for $[Co(NH_3)_6]Cl_3$. For the less stable ammines such as $[Cu(NH_3)_4]^{2+}$ (log $k_{average}$ 3·3), a Raman frequency of 419 cm.$^{-1}$ has been reported,[7] and as this ammine has the same symmetry as the platinous tetrammine with Raman frequencies of 538 and 526 cm.$^{-1}$,[8] it would not be unreasonable to expect an infrared-active frequency near 400 cm.$^{-1}$. This is supported by examination of the infrared spectrum of $[Cu(NH_3)_4]Cl_2$, which shows evidence of an absorption band just below 400 cm.$^{-1}$ but which could not be identified more definitely as it is below the range of the potassium bromide prism. On this basis 110 cm.$^{-1}$ would correspond to a change of about 3 in the value of log $k_{average}$, and the 26 cm.$^{-1}$ change in frequency when NH_3 is replaced by C_2H_4 would correspond to a change in log k of about 0·7.

From these considerations it is clear that, in these cases, notably that of ethylene, and to a lesser extent of diethyl sulphide, the bond weakening produced is sufficient to have a significant effect on the tendency of the *trans*-NH_3 group to dissociate. This does not imply that dissociation is the controlling factor in determining the extent of the *trans*-directive power of ligands, but that in such cases the possibility of its having a contributory effect should be considered.

Experimental

Most of the spectra in the potassium bromide region from 720 to 450 cm.$^{-1}$ were obtained by using a modified Hilger D 209 spectrometer as a single-beam instrument. For the spectra of $[Co(NH_3)_6]Cl_3$ and $[Cu(NH_3)_4]Cl_2$ a Hilger H 800 spectrometer was used to extend the region examined to 400 cm.$^{-1}$. The compounds were all examined as very concentrated Nujol mulls, since the ν M–N absorption frequencies are extremely weak. The spectra in the rock-salt region were obtained by using a Perkin-Elmer double beam spectrometer.

Preparation of Compounds.—*cis*-$Pt(NH_3)_2Cl_2$ was prepared by Jörgensen's method. Its spectrum showed no indication of the absorption peaks at 1288 and 828 cm.$^{-1}$ found for the *trans*-isomer.

cis-$Pt(NH_3)_2(NO_2)Cl$ was precipitated by addition of aqueous ammonia to $K[Pt(NO_2)Cl_3]$ [Found: N, 13·65. Calc. for $Pt(NH_3)_2(NO_2)Cl$: N, 13·5%]. *cis*-$Pt(NH_3)_2(NO_2)_2$ was prepared by addition of aqueous ammonia to a solution of $K_2Pt(NO_2)_4$. $K[Pt(C_2H_4)Cl_3].H_2O$ was obtained as described by Chatt *et al.*[9] and was converted into *trans*-$Pt(C_2H_4)(NH_3)Cl_2$ by addition of aqueous ammonia.

cis- and *trans*-$(Et_2S)_2PtCl_2$ were prepared as described by Angell, Drew, and Wardlaw.[10] The *cis*-isomer on treatment with Na_2PtCl_4 produced the bridged compound described by Chatt and Venanzi;[11] this was then converted into *trans*-$Pt(Et_2S)(NH_3)Cl_2$ by addition of the theoretical amount of ammonia in 95% alcohol. The identity of the product was confirmed by measurement of the infrared spectra in the rock-salt and the potassium bromide region. These spectra indicated the presence of co-ordinated NH_3 and Et_2S groups, and the frequency due to the Pt–N vibration is smaller than for the platinous chloroammines [Found: C, 12·7; H, 3·6. Calc. for $Pt(Et_2S)(NH_3)Cl_2$: C, 12·8; H, 3·5%].

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[7] Hibben, "The Raman Effect and its Chemical Applications," Reinhold, New York, 1939, p. 462.
[8] Mathieu, *J. Chim. phys.*, 1939, **36**, 308.
[9] Chatt and Duncanson, *J.*, 1953, 2939.
[10] Angell, Drew, and Wardlaw, *J.*, 1930, 349.
[11] Chatt and Venanzi, *J.*, 1955, 2787, 3858.

866. *Molecular Polarisation in Ternary Systems comprising Benzene, Pyridine, and an Alcohol.*

By D. Cleverdon, G. B. Collins, and J. W. Smith.

The apparent molecular polarisations of *n*- and *tert.*-butyl alcohol and of diphenylmethanol at zero concentration in various benzene–pyridine mixtures, and of pyridine at zero concentration in various mixtures of benzene with the alcohols, have been determined. By assuming that the active masses of the alcohols, pyridine, and association complexes can be represented satisfactorily by their concentrations in mole/c.c., the approximate equilibrium constants for the association of pyridine with the monomeric alcohol molecules, and the effective molecular polarisations of the association complexes, have been calculated. The results are discussed in relation to the probable electron distibutions in the alcohol molecules.

The fact that the presence of pyridine modifies considerably the courses of the reactions of certain alcohols with, *e.g.*, acetyl chloride, suggests that pyridine may associate with these alcohols. In 1947 it was pointed out [1] that any such association should cause the dielectric polarisation of a solution containing both an alcohol and pyridine in an inert solvent to be greater than the value calculated from the molecular polarisations of the components. An effect of the type predicted was observed for a number of alcohols in benzene solution, and the augmentation of the polarisation above the value calculated from the amounts of alcohol and pyridine present was shown to increase progressively with the concentrations of both the alcohol and pyridine.[2] On the grounds of the chemical behaviour of their derivatives, a series of alkyl and substituted alkyl groups was arranged in the order of their electron-releasing properties, and it was thought possible that the increases in polarisation observed for the alcohols derived from these groups, when studied under comparable conditions, might follow a similar order.[1] This aspect of the subject has had to be deferred, however, until the effect has been studied in more detail for simple alcohols so as to elucidate the quantitative aspects of the increment of the polarisation. With this object in view the dielectric polarisations of mixtures of benzene and pyridine with *n*- and *tert.*-butyl alcohol and with diphenylmethanol have now been studied in detail.

To investigate systems comprising two solutes A and B, which associate with one another but not with the solvent S, it is desirable to determine the limiting values of the molecular polarisation of A at zero concentration in various mixtures of B and S, and also of the molecular polarisation of B at zero concentration in mixtures of A and S. The study of the systems from the two points of view, however, does not necessitate complete duplication of the experimental work, as once data have been obtained for solutions of A in a number of mixtures of B and S these can be used to provide corresponding data for solutions of B in mixtures of A and S. If the weight fractions of the three components are w_A, w_B, and w_S, then $w_A + w_B + w_S = 1$. If a mixture is regarded as a solution of A in a solvent $B + S$, then w_B', the weight fraction of B in the solvent mixture, is $w_B/(w_B + w_S)$, and therefore $w_B = w_B'(1 - w_A)$. Alternatively, if the system is regarded as a solution of B in a solvent $A + S$, it follows that $w_A = w_A'(1 - w_B)$, where w_A' is the weight fraction of A in the solvent. Combining these expressions we obtain :

$$w_A = w_A' \frac{1 - w_B'}{1 - w_A'w_B'} \quad \text{and} \quad w_B = w_B' \frac{1 - w_A'}{1 - w_A'w_B'}$$

If solutions of A in constant mixtures of B and S have been studied, the values of w_B' have been fixed when making the solvent mixtures. If a set of convenient values be chosen for w_A' the corresponding values of w_A may be calculated for each mixture, and the specific polarisations of the solutions of those concentrations determined by interpolation of the

[1] Cleverdon, Ph.D. Thesis, London, 1947.
[2] Cleverdon and Smith, *Chem. and Ind.*, 1948, 29.

existing data. It remains only to calculate the set of values of w_B to complete the polarisation data equivalent to those for a series of solutions of B in mixtures of A and S in the chosen proportions.

The general case of two substances A and B, which form an unstable compound AB but do not react with the solvent S, has been discussed previously.[3] If the active masses of these substances can be represented by their concentrations in mole/c.c., the apparent limiting value of the molecular polarisation of A at zero concentration in a constant mixture of B and S, $(P_{A_\infty})_{BS}$, is given by:

$$\frac{\Delta P}{(P_{A_\infty})_{BS} - (P_{A_\infty})_S} = \frac{M_B}{Kw_B'd_{BS}} + 1$$

where M_B is the molecular weight of B, d_{BS} the density of the solvent mixture, K the association constant of the complex AB, and $\Delta P = (P_{AB_\infty})_S - (P_{A_\infty})_S - (P_{B_\infty})_S$, the last three functions being the limiting values of the molecular polarisations of AB, A, and B, respectively, at zero concentration in the solvent S. It follows, therefore, that a plot of $1/\{(P_{A_\infty})_{BS} - (P_{A_\infty})_S\}$ against $M_B/w_B'd_{BS}$ should be linear, with a slope $1/K\Delta P$ and an intercept on the axis for the former of $1/\Delta P$. Further, this should superpose upon the corresponding plot of $1/\{(P_{B_\infty})_{AS} - (P_{B_\infty})_S\}$ against $M_A/w_A'd_{AS}$ derived from data for solutions of B in solvents comprising mixtures of A and S.

The assumptions on which this method is based should be roughly true for the case of an alcohol in a series of constant mixtures of pyridine and benzene. When the alcohol approaches zero concentration in these A-in-BS systems the conditions become such that interaction occurs only between pyridine and monomeric alcohol molecules. When the $(P_{B_\infty})_{AS}$ values for pyridine in constant mixtures of an alcohol and benzene ("B-in-AS" systems) are studied, however, the alcohol is present both as single molecules and as associated molecules of various degrees of complexity. As the extent of this association differs from one solvent mixture to another the results obtained in different series of measurements relate to the interaction of pyridine molecules with alcohols in different states of complexity. Hence the plots for the B-in-AS systems cannot be expected to superpose upon those for the A-in-BS systems.

The polarisation results obtained for the systems studied are summarised in Table 1, where α and β are the limiting values of $d\varepsilon/dw$ and dv/dw, respectively, at zero concentration. The values of $(P_{A_\infty})_{BS}$ and $(P_{B_\infty})_{AS}$ shown are the mean figures from at least three methods of extrapolation, and the maximum divergences from the mean values are indicated. The results for the series of solutions of *n*-butyl alcohol in a pyridine–benzene mixture fall well in line with the remaining data for this system, derived by the indirect procedure.

In each system the apparent molecular polarisation values at zero concentration increase progressively with increasing concentration of pyridine or alcohol in the solvent mixture. On the other hand the association does not seem to affect appreciably the refractivities of the mixtures, as the apparent values of the molecular refractions of the solutes show no systematic change with the composition of the solvent. The effective specific volumes of the solutes, as given by $v_{BS} + \beta$ or $v_{AS} + \beta$, indicate that in each system the association is accompanied by a decrease in volume. A decrease in effective specific volume also accompanies the association of alcohols alone in benzene solution.[4]

If P_{E+A} is assumed to be represented by $[R_D]$, the results for solutions of pyridine in benzene lead to a dipole moment of 2·20 D, in accordance with previous values[5–7] obtained from measurements on benzene solutions (2·23, ~2·2, 2·20) and close to the value (2·15 D) obtained from microwave-absorption measurements on the vapour.[8]

[3] Few and Smith, *J.*, 1949, 2781.
[4] Boud, Cleverdon, Collins, and Smith, *J.*, 1955, 3893.
[5] Goethals, *Rec. Trav. chim.*, 1935, **54**, 299.
[6] Hückel, *Ber.*, 1944, **77**, 810.
[7] Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79.
[8] De More, Wilcox, and Goldstein, *J. Chem. Phys.*, 1954, **22**, 876.

TABLE 1. *Summary of polarisation data.*

$100w_B$	v_{BS}	α	β	$(P_{A\infty})_{BS}$ (c.c.)	$(P_{A\infty})_{BS} - (P_{A\infty})_S$ (c.c.)	$[R_D]_A$ (c.c.)
			n-Butyl alcohol in benzene–pyridine.			
0·000	1·14458	3·77	0·133	81·0 ± 0·3	—	22·0
1·000	1·14328	—	—	94·3 ± 0·1	13·3	—
2·000	1·14192	—	—	103·9 ± 0·2	22·9	—
2·833	1·14083	6·15	0·130	109·5 ± 0·3	28·5	22·1
3·000	1·14059	—	—	110·6 ± 0·2	29·6	—
4·000	1·13926	—	—	115·2 ± 0·3	34·2	—
5·000	1·13793	—	—	118·7 ± 0·2	37·7	—
6·000	1·13660	—	—	121·4 ± 0·1	40·4	—
			tert.-Butyl alcohol in benzene–pyridine			
0·000	1·14458	3·65	0·206	80·5 ± 0·2	—	22·6
1·244	1·14286	4·18	0·207	87·2 ± 0·3	6·7	22·7
2·440	1·14133	4·64	0·206	92·3 ± 0·4	11·8	22·6
3·738	1·13957	5·06	0·206	96·4 ± 0·3	15·9	22·7
6·541	1·13587	5·69	0·206	100·7 ± 0·3	20·2	22·6
6·871	1·13547	5·86	0·204	102·2 ± 0·4	21·7	22·6
9·166	1·13242	6·20	0·205	103·1 ± 0·3	22·6	22·6
			Diphenylmethanol in benzene–pyridine.			
0·000	1·14458	1·780	−0·246	111·0 ± 0·2	—	57·7
1·477	1·14260	3·157	−0·249	155·6 ± 0·2	44·6	57·7
1·907	1·14205	3·422	−0·249	163·4 ± 0·2	52·4	57·5
2·763	1·14089	3·850	−0·249	175·3 ± 0·3	64·3	57·5
4·266	1·13884	4·364	−0·250	187·9 ± 0·1	76·9	57·6

$100w_A$	v_{AS}	α	β	$(P_{B\infty})_{AS}$ (c.c.)	$(P_{B\infty})_{AS} - (P_{B\infty})_S$ (c.c.)	$[R_D]_B$ (c.c.)
			Pyridine in benzene–n-butyl alcohol.			
0·000	1·14455	$6·67_8$	−0·133	123·2 ± 0·2	—	24·1
0·923	1·14577	7·79	−0·140	138·4 ± 0·2	15·2	24·1
1·250	1·14616	$8·14_3$	−0·142	143·2 ± 0·3	20·0	24·0
1·866	1·14698	8·90	−0·146	153·0 ± 0·3	29·8	24·0
2·538	1·14777	9·69	−0·150	163·7 ± 0·5	40·5	24·1
3·564	1·14895	10·92	−0·154	177·9 ± 0·5	54·7	24·0
4·350	1·14983	11·83	−0·157	188·8 ± 0·6	65·6	24·0
			Pyridine in benzene–tert.-butyl alcohol.			
1·000	1·14659	—	—	130·2 ± 0·2	7·0	—
2·000	1·14850	—	—	137·2 ± 0·3	14·0	—
3·000	1·15034	—	—	144·4 ± 0·4	21·2	—
4·000	1·15214	—	—	151·6 ± 0·4	28·4	—
5·000	1·15388	—	—	159·1 ± 0·5	35·9	—
			Pyridine in benzene–diphenylmethanol.			
1·000	1·14210	—	—	139·3 ± 0·1	16·1	—
2·000	1·13964	—	—	153·0 ± 0·0	29·8	—
3·000	1·13718	—	—	165·1 ± 0·1	41·9	—
4·000	1·13472	—	—	175·5 ± 0·3	52·3	—
5·000	1·13226	—	—	184·1 ± 0·3	60·9	—
6·000	1·12980	—	—	190·5 ± 0·5	67·3	—

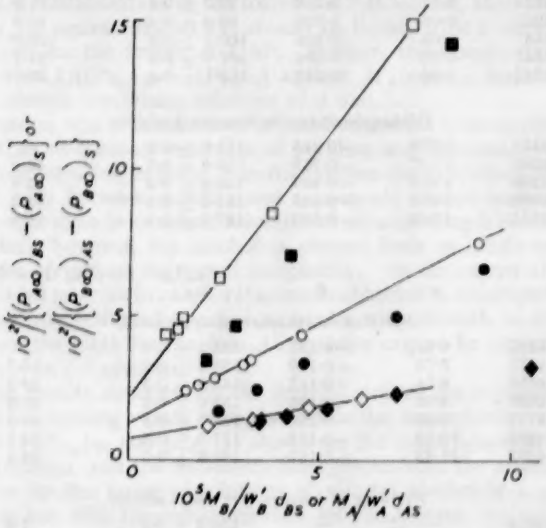
The results of plotting $1/\{(P_A)_{BS} - (P_A)_S\}$ against $M_B v_{BS}/w_B'$ are shown in the Figure. For each of the A in BS systems the points are satisfactorily linear, although there are slight indications of deviations at low values of $M_B v_{BS}/w_B'$, corresponding to high pyridine concentrations, where the assumptions regarding the ideality of behaviour are less justified. The best straight lines as deduced by the least-squares method have the slopes and intercepts shown in Table 2. The values of K and of the dipole moments μ_{AB} of the complexes deduced from these results are also included in the Table.

TABLE 2. *Association constants in benzene solution, and dipole moments of complexes of pyridine with alcohols.*

Alcohol	$1/K\Delta P$ ($\times 10^6$)	$1/\Delta P$ ($\times 10^4$)	K ($\times 10^{-2}$)	ΔP (c.c.)	$(P_{AB_\infty})_S$ (c.c.)	$[R_{AB}]_S$ (c.c.)	μ_{AB} (D)
n-Butyl alcohol	683	135	20	74	278	46	3·37
tert.-Butyl alcohol	1745	210	12	48	252	47	3·16
Diphenylmethanol	239	77	32	130	364	82	3·71

The results for the pyridine–diphenylmethanol *B*-in-*AS* system lie on the same line as those for the corresponding *A*-in-*BS* system so long as the concentration of alcohol is low, under which conditions the alcohol is essentially monomeric.[4] This seems to confirm the essential validity of the method for studying such association by molecular polarisation measurements. At the highest diphenylmethanol concentrations used, however, association of the alcohol becomes appreciable, and divergences from collinearity with the *A*-in-*BS*

Plots of $1/\{(P_{A_\infty})_{BS} - (P_{A_\infty})_S\}$ *against* $M_B/w_B'd_{BS}$ *and of* $1/\{(P_{B_\infty})_{AS} - (P_{B_\infty})_S\}$ *against* $M_A/w_A'd_{AS}$.



○ *n-Butyl alcohol in benzene–pyridine.*
□ tert.-*Butyl alcohol in benzene–pyridine.*
◇ *Diphenylmethanol in benzene–pyridine.*
● *Pyridine in benzene–n-butyl alcohol.*
■ *Pyridine in benzene–tert.-butyl alcohol.*
◆ *Pyridine in benzene–diphenylmethanol.*

data occur. It is not surprising that the results for the *B*-in-*AS* systems involving *n*- and *tert.*-butyl alcohol show much greater divergences from those for the corresponding *A*-in-*BS* system, as their association is considerable even in 1% solutions in benzene. The data fall on lines which are almost parallel to those for the *A*-in-*BS* systems, with slopes 708 and 1700 $\times 10^{-7}$, respectively. For each *B*-in-*AS* system the $(P_{B_\infty})_{AS} - (P_{B_\infty})_S$ values are greater than would be expected from the data for the *A*-in-*BS* system by an amount which increases progressively with increasing concentration of alcohol in the solvent mixture. As the association of alcohols in benzene solution seems to lead to the production of polymeric rather than dimeric molecules,[4] pyridine would be expected to associate more readily with dimeric and polymeric alcohol molecules than with monomeric molecules. This would account qualitatively for the results observed, although the matter is further complicated by the fact that association with dimeric and polymeric molecules will lead to aggregates of different average moment from those formed with monomeric alcohol molecules.

The values of the product $K\Delta P$, being obtained from the slopes of the plots for the

A-in-*BS* systems, should be fairly accurate. The separate K and ΔP values, however, are subject to much greater error, and the values of μ_{AB} calculated from the latter have a probable error of about $\pm 0{\cdot}05$ D. The values of K obtained indicate that *n*-butyl alcohol tends to associate with pyridine to a slightly greater extent than does *tert.*-butyl alcohol. This behaviour is parallel to the association of the alcohol molecules with one another in benzene solution. On the other hand, although only slightly associated itself at low concentrations in benzene solution, diphenylmethanol associates with pyridine more readily than do either of the butyl alcohols. Further, the ΔP value, which gives the difference between the molecular polarisation of the complex and the sum of the molecular polarisations of the two separate compounds, is also greatest for diphenylmethanol and least for *tert.*-butyl alcohol.

In the association complex the axis of the pyridine dipole is collinear with the H–O bond of the alcohol molecule and hence, if no electron displacements occur within the molecules as a result of the association, the dipole moment of the complex should be given by $\mu_{AB}^2 = \mu_A^2 + \mu_B^2 + 2\mu_A\mu_B \cos\theta$, where θ is the angle of inclination of the dipole axis of the alcohol molecule to the O–H bond. The values obtained for μ_A, μ_B, and μ_{AB} lead to angles θ of 60°, 72°, and 29° in the *n*-butyl alcohol, *tert.*-butyl alcohol, and diphenylmethanol molecule, respectively.

Although the oxygen bond angle in the alcohols (110½° in methyl alcohol) is greater than that in water (104½°), in which the effective bond moment is 1·5 D, the forms of the lone-pair orbitals are such that the contributions of the lone-pair electrons to the dipole moments are almost equal in water and in the alcohols. On the other hand the change in state of hybridisation of the bonding orbitals should lead to a slightly smaller H–O bond moment in an alcohol compared with that in water. The value of θ found for *n*-butyl alcohol can be accounted for by effective components to the moment of 1·55 and 1·38 D along the C–O and H–O bonds respectively. The above considerations together with an inductive effect in the alkyl group render these values not unreasonable.

Although the dipole moment of *tert.*-butyl alcohol is about the same as that for *n*-butyl alcohol, it is probable that the electron-density distribution is very different in the two molecules. This is shown, for instance, by the difference between the modes of interaction of the two compounds with hydrogen chloride. As compared with *n*-butyl alcohol there is likely to be an effective increase of the component of the moment along the C–O bond and a corresponding decrease in the component of the moment along the H–O bond.

These effects will cause the axis of the dipole in the *tert.*-butyl alcohol molecule to have a greater angle of inclination to the H–O bond than has the axis of the moment of *n*-butyl alcohol. Although the results are not sufficiently accurate to be used as a real measure of θ they suggest that in the formation of the complexes of these alcohols with pyridine there is no appreciable modification of the electron-density ditribution originally present in the separate molecules.

It seems highly improbable, however, that the dipole in the diphenylmethanol molecule is inclined to the H–O bond at an angle as small as 29°, as this would correspond with components of 1·70 and 0·83 D along the H–O and the C–O bond, respectively, in the isolated molecule. A much more plausible explanation for the relatively high value found for the moment of the complex with pyridine is that in this system the association between the molecules causes a modification of the electron distribution in the component molecules. It has been shown [9] that the apparent molecular polarisations of primary and secondary aromatic amines in dioxan solution are greater than in benzene, whilst for aliphatic amines the values obtained in the two solvents are almost equal. As dioxan itself has zero dipole moment, hydrogen bonding between an oxygen atom of a dioxan molecule and an amino-hydrogen atom would not, *per se*, lead to an increase in the dielectric polarisation of the system. Hence polarisation measurements do not prove the non-existence of association between dioxan and aliphatic amines, but simply indicate that, if this association occurs, it is not accompanied by any appreciable change in the electron-density distribution in the two molecules. For aromatic amines the difference between the apparent dipole

[9] Few and Smith, *J.*, 1949, 753; Smith, *J.*, 1950, 3532; 1953, 109.

moments in dioxan and in benzene solution must be a consequence of the hydrogen bonding, and can be correlated with the readiness with which mesomeric displacements can occur in the amine molecule. Similar displacements may account for the results now obtained with diphenylmethanol. Since this compound reacts with hydrochloric acid by the same mechanism as *tert.*-butyl alcohol, it is probable that in the isolated molecule there is a tendency for electron density to be donated from the benzene rings towards the adjoining carbon atom. This leads to an increased component to the moment directed roughly along the C–O bond, as in *tert.*-butyl alcohol. On association with a pyridine molecule, however, this effect will be easily reversed, leading to a resultant moment for the complex in excess of the value which would be expected from vector addition of the values for the separate molecules.

Since this work was completed, Sutton and his co-workers [10] have used partitioning between the liquid and vapour phases to investigate complex formation between a volatile reactant and an involatile one in a volatile solvent. For *cyclo*hexane solutions of trimethylamine and *n*-heptyl alcohol the association constant for hydrogen-bond formation was found to be 35×10^2 (mole/c.c. units) which is comparable with our values for the butyl alcohols and pyridine, whilst for trimethylamine and triphenylmethanol it was found to have a higher value (120×10^2), as is to be expected from our result for diphenylmethanol. The finding that when K values determined in this way are combined with polarisation data for systems involving phenols and trimethylamine there is an increase in moment ($\Delta\mu$) as compared with the vector sum of the moments of the reactants parallels our observation with diphenylmethanol and pyridine. Further, the fact that $(\Delta\mu)^2$ is a fairly linear function of K appears to be somewhat analogous to the rough proportionality shown between the values of K and ΔP in Table 2.

Experimental

Materials.—Benzene, *n*- and *tert.*-butyl alcohol, and diphenylmethanol were purified as described previously.[4] Laboratory-reagent pyridine was dried (NaOH) and distilled through a 20-plate column; the middle fraction was refluxed from three successive portions of potassium permanganate and then from freshly ignited barium oxide; it was finally distilled from barium oxide in dry nitrogen and had b. p. 115·5°/762 mm., d_4^{25} 0·97786, n_D^{25} 1·5071.

Apparatus and Methods.—The dielectric constants were measured with the resonance apparatus described by Few, Smith, and Witten [11] relative to a value of 2·2725 for the dielectric constant of benzene at 25°. The use of the more recent value [12] of 2·2741 makes no perceptible difference to the conclusions. The refractive indices were measured with a Hilger Abbé refractometer. In the systems involving *tert.*-butyl alcohol and diphenylmethanol the measurements were concentrated on series of solutions of the alcohol in various pyridine–benzene mixtures, but, to facilitate interpolation of the results, most of the measurements on the system containing *n*-butyl alcohol were made on series of solutions of pyridine in mixtures of benzene with the alcohol. All measurements were made at 25·0°. The results are recorded in Table 3.

Table 3. *Polarisation data.*

Pyridine in benzene.

$100w_2$	ε	v	n_D	p	P_2	R_2
0·0000	2·2725	1·14458	1·4979	0·34089	—	—
0·7945	2·3258	1·14353	1·4981	0·35048	122·5	24·6
2·2190	2·4228	1·14166	1·4983	0·36727	121·0	24·3
3·8926	2·5386	1·13946	1·4984	0·38628	119·2	24·0
4·4362	2·5771	1·13868	1·4985	0·39234	118·7	24·1
5·0702	2·6218	1·13784	1·4986	0·39927	118·0	24·1
6·4325	2·7197	1·13601	1·4987	0·41393	116·8	24·0

$\varepsilon = 2{\cdot}2725 + 6{\cdot}675w_2 + 4{\cdot}26w_2^2$. $n_D^2 = 2{\cdot}2437 + 0{\cdot}04w_2$.

$v = 1{\cdot}4458 - 0{\cdot}133w_2$.

P_2 by direct extrapolation = 123·2 c.c.; from parameters = 123·16 c.c. $[R_D]_2 = 24{\cdot}05$ c.c. Taking $P_{E+A} = [R_D]$, $\mu = 2{\cdot}20_2$ D.

[10] Denyer, Gilchrist, Pegg, Smith, Tomlinson, and Sutton, *J.*, 1955, 3889; Hulett, Pegg, and Sutton, *J.*, 1955, 3901.

[11] Few, Smith, and Witten, *Trans. Faraday Soc.*, 1952, **48**, 211.

[12] Hartshorn, Parry, and Essen, *Proc. Phys. Soc.*, 1955, **68**, *B*, 422.

TABLE 3. (*Continued.*)

n-Butyl alcohol in pyridine–benzene.

$100w_B$	$100w_A$	ε	v	n_D	p	P_A	R_A
4·410	0·0000	2·5758	1·13872	—	0·39215	—	—
	2·1650	2·7343	1·14095	—	0·41796	117·4	—
	4·0562	2·8756	1·14299	—	0·43970	115·9	—
	6·1995	3·0227	1·14528	—	0·46122	111·4	—
	7·9983	3·1589	1·14707	—	0·48003	110·5	—
2·833	0·0000	2·4650	1·14083	1·4981	0·37432	—	—
	0·9843	2·5270	1·14204	1·4970	0·38522	109·9	22·7
	2·8924	2·6530	1·14429	1·4946	0·40651	110·2	22·2
	2·9991	2·6598	1·14436	1·4943	0·40762	110·1	21·9
	3·0916	2·6662	1·14449	1·4941$_5$	0·40867	110·1	21·9
	4·5501	2·7627	1·14607	1·4926	0·42417	109·0	22·2
	4·8752	2·7840	1·14647	1·4922	0·42753	108·7	22·2

Pyridine in n-butyl alcohol–benzene.

$100w_A$	$100w_B$	ε	v	n_D	p	P_B	R_B
0·9233	0·0000	2·3085	1·14577	1·4967	0·34797	—	—
	0·6650	2·3600	1·14483	1·4968$_5$	0·35711	136·2	24·4
	1·3439	2·4118	1·14384	1·4969$_5$	0·36604	133·9	24·0
	2·1411	2·4718	1·14280	1·4970$_5$	0·37613	131·6	24·0
	2·9471	2·5323	1·14168	1·4972	0·38598	129·5	24·0
	4·7860	2·6694	1·13921	1·4974$_5$	0·40729	125·6	24·1
	6·4394	2·7933	1·13698	1·4977	0·42538	122·6	24·1
1·250	0·0000	2·3222	1·14616	1·4962	0·35062	—	—
	0·9771	2·4009	1·14487	1·4963	0·36444	139·6	23·9
	1·8384	2·4688	1·14362	1·4964	0·37589	136·4	23·8
	2·9127	2·5512	1·14218	1·4966	0·38929	132·7	24·0
	3·7391	2·6142	1·14103	1·4968	0·39917	130·4	24·0
	5·0759	2·7156	1·13918	1·4970	0·41445	127·2	24·0
	5·7741	2·7686	1·13825	1·4971	0·42215	125·7	24·0
1·866	0·0000	2·3479	1·14698	1·4955	0·35558	—	—
	0·6028	2·4016	1·14608	1·4956	0·36495	151·1	23·7
	1·2421	2·4557	1·14518	1·4957	0·37414	146·4	23·9
	2·2688	2·5409	1·14366	1·4959$_5$	0·38809	141·5	24·0
	2·9854	2·5981	1·14268	1·4961	0·39715	138·3	24·1
	5·0322	2·7601	1·13988	1·4964	0·42148	131·7	24·0
	6·2873	2·8582	1·13813	1·4966$_5$	0·43532	128·5	24·1
2·538	0·0000	2·3766	1·14777	1·4946	0·36102	—	—
	0·5823	2·4325	1·14693	1·4947	0·37067	159·6	24·0
	1·3289	2·5009	1·14583	1·4949	0·38210	154·0	24·1
	2·1123	2·5698	1·14473	1·4950	0·39324	149·2	24·0
	2·8671	2·6341	1·41366	1·4952	0·40329	145·2	24·0
	4·5834	2·7757	1·14124	1·4955	0·42434	137·8	24·1
	6·7647	2·9508	1·13822	1·4958$_5$	0·44850	130·8	24·1
3·564	0·0000	2·4211	1·14895	1·4934$_5$	0·36932	—	—
	0·6522	2·4907	1·14794	1·4936	0·38106	171·6	23·7
	1·2361	2·5500	1·14709	1·4937	0·39077	166·5	23·8
	2·3167	2·6530	1·14554	1·4939	0·40695	157·7	23·9
	2·8161	2·6992	1·14483	1·4941	0·41396	154·6	24·1
	4·5346	2·8500	1·14236	1·4944$_5$	0·43574	145·1	24·0
	6·9125	3·0490	1·13901	1·4948$_5$	0·46223	135·5	24·1
4·350	0·0000	2·4545	1·14983	1·4924	0·37544	—	—
	0·5816	2·5217	1·14892	1·4925	0·38665	182·1	23·6
	1·3242	2·6028	1·14780	1·49275	0·39969	174·5	24·0
	2·0719	2·6790	1·14676	1·4929	0·41150	167·4	24·1
	3·2037	2·7886	1·14508	1·4931	0·42770	158·7	24·0
	4·6780	2·9225	1·14292	1·4934$_5$	0·44637	149·6	24·0
	6·7755	3·1042	1·13997	1·4938$_5$	0·46995	140·0	24·0

tert.-Butyl alcohol in pyridine–benzene.

$100w_B$	$100w_A$	ε	v	n_D	p	P_A	R_A
1·244	0·0000	2·3565	1·14286	1·4980	0·35585	—	—
	0·5432	2·3793	1·14397	1·4972	0·36031	87·1	22·9
	0·9696	2·3975	1·14481	1·4965$_5$	0·36381	87·2	22·8
	1·8620	2·4360	1·14655	1·4953	0·37116	87·3	23·0
	2·9705	2·4827	1·14858	1·4936	0·37990	86·4	22·7
	4·1819	2·5315	1·15076	1·4919	0·38892	85·0	22·8
	5·4530	2·5801	1·15299	1·4900	0·39777	83·4	22·6

TABLE 3. (*Continued.*)

tert.-*Butyl alcohol in pyridine–benzene.*

$100w_B$	$100w_A$	ϵ	v	n_D	p	P_A	R_A
2·440	0·0000	2·4382	1·14133	1·4983	0·36985	—	—
	0·4540	2·4594	1·14219	1·4976	0·37379	91·8	22·4
	1·0004	2·4854	1·14326	$1·4967_5$	0·37860	92·3	22·5
	1·7855	2·5232	1·14477	1·4956	0·38550	92·4	22·6
	2·3921	2·5518	1·14595	1·4947	0·39068	92·0	22·6
	3·9556	2·6235	1·14876	$1·4925_5$	0·40338	90·2	22·7
	5·1362	2·6749	1·15082	$1·4909_5$	0·41232	88·7	22·8
3·738	0·0000	2·5282	1·13957	1·4984	0·38459	—	—
	0·5667	2·5571	1·14066	$1·4975_5$	0·38975	96·0	22·7
	1·0785	2·5838	1·14168	1·4968	0·39447	96·4	22·7
	1·5541	2·6089	1·14262	1·4961	0·39888	96·6	22·8
	2·6278	2·6648	1·14460	1·4946	0·40850	95·9	22·8
	3·8606	2·7266	1·14688	1·4928	0·41894	94·5	22·8
	5·5571	2·8090	1·14981	$1·4904_5$	0·43252	92·4	22·7
6·541	0·0000	2·7284	1·13587	1·4987	0·41521	—	—
	0·5172	2·7581	1·13691	1·4980	0·42009	100·7	23·4
	0·9789	2·7846	1·13775	1·4973	0·42437	100·2	22·8
	1·6789	2·8263	1·13916	$1·4962_5$	0·43107	100·8	22·8
	2·6182	2·8821	1·14087	$1·4947_5$	0·43982	100·5	22·5
	3·7618	2·9489	1·14293	1·4932	0·45009	99·5	22·5
	5·3449	3·0387	1·14574	1·4910	0·46358	97·9	22·6
6·871	0·0000	2·7510	1·13547	1·4986	0·41848	—	—
	0·5059	2·7808	1·13646	1·4980	0·42332	102·0	23·9
	1·0360	2·8126	1·13747	1·4972	0·42842	102·1	23·2
	1·7573	2·8575	1·13882	1·4961	0·43549	102·8	22·8
	2·6889	2·9120	1·14056	1·4947	0·44396	101·3	22·7
	3·5443	2·9624	1·14209	1·4934	0·45164	100·4	22·5
	5·6388	3·0832	1·14581	1·4904	0·46958	98·2	22·5
9·166	0·0000	2·9202	1·13242	$1·4991_5$	0·44195	—	—
	0·5689	2·9557	1·13354	1·4983	0·44734	103·0	22·6
	1·3042	3·0023	1·13497	1·4972	0·45431	103·0	22·6
	1·6229	3·0231	1·13557	1·4967	0·45736	103·2	22·5
	2·6476	3·0892	1·13748	—	0·46696	102·8	—
	3·8051	3·1616	1·13957	1·4936	0·47723	101·5	22·6
	4·9980	3·2391	1·14165	1·4918	0·48792	100·9	22·5

Diphenylmethanol in pyridine–benzene.

1·477	0·0000	2·3724	1·14260	$1·4980_5$	0·35864	—	—
	0·5942	2·3910	1·14110	1·4986	0·36148	154·1	57·7
	1·4323	2·4170	1·13901	$1·4993_5$	0·36541	153·1	57·7
	2·4494	2·4475	1·13651	$1·5002_5$	0·36989	150·7	57·7
	3·5960	2·4808	1·13369	1·5012	0·37466	148·2	57·5
	4·4428	2·5049	1·13163	1·5020	0·37803	146·5	57·7
	5·6949	2·5400	1·12853	1·5030	0·38281	144·3	57·3
1·907	0·0000	2·4018	1·14205	1·4983	0·36370	—	—
	0·5143	2·4193	1·14077	1·4987	0·36637	162·8	56·4
	1·5728	2·4548	1·13816	$1·4996_5$	0·37169	160·6	57·3
	2·2371	2·4762	1·13645	1·5003	0·37479	158·4	57·5
	3·0757	2·5029	1·13439	1·5010	0·37861	156·4	57·5
	4·5423	2·5483	1·13076	1·5021	0·38492	153·1	56·9
	5·9192	2·5892	1·12735	$1·5033_5$	0·39039	150·1	57·1
2·763	0·0000	2·4600	1·14089	1·4983	0·37347	—	—
	0·2931	2·4712	1·14012	$1·4985_5$	0·37515	174·1	56·7
	0·5458	2·4809	1·13949	$1·4987_5$	0·37659	174·1	56·7
	2·0408	2·5366	1·13581	$1·5000_5$	0·38471	170·3	57·3
	3·6932	2·5952	1·13172	1·5015	0·39287	165·6	57·3
	4·5092	2·6235	1·12969	$1·5022_5$	0·39668	163·6	57·5
4·266	0·0000	2·5649	1·13884	1·4985	0·39041	—	—
	0·2728	2·5769	1·13815	$1·4987_5$	0·39213	188·2	58·2
	0·6439	2·5929	1·13723	1·4991	0·39441	186·6	57·8
	0·8541	2·6018	1·13672	1·4993	0·39567	185·5	57·8
	1·8917	2·6457	1·13418	1·5001	0·40177	182·6	57·1
	3·1605	2·6978	1·13103	1·5013	0·40875	178·9	57·3
	4·6501	2·7568	1·12745	1·5026	0·41639	174·9	57·5

In none of the mixtures studied was ε a linear function of w_A (or w_B) and hence, to minimise errors in the relative values of $(P_{A_\infty})_{BS}$ or $(P_{B_\infty})_{AS}$ derived, the methods used in the extrapolation to zero concentration included, not only the determination of the limiting value of $(\Delta\varepsilon/w_A)_{BS}$ and $(\Delta v/w_A)_{BS}$, but also the limiting values of $(\Delta\varepsilon/w_A)_{BS} - (\Delta\varepsilon/w_A)_B$, $(P_A)_{BS} - (P_A)_S$, $(P_A)_{BS}' - (P_A)_{BS}$ for successive solvent mixtures and $(P_A)_{BS}'/(P_A)_{BS}$ for successive solvent mixtures. A series of extrapolated values of $(P_{A_\infty})_{BS}$ were thereby obtained, the spread indicating the probable error in the final average value taken. For the derived data only the functions involving the molecular polarisation values were used.

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867. *Dielectric Polarisation Studies of the Formation of Hydrogen-bond Complexes by Alcohols.*

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The apparent molecular polarisations of *n*- and *tert.*-butyl alcohols at zero concentration in various benzene–triethylamine mixtures, and of triethylamine at zero concentration in various mixtures of benzene with the alcohols, have been determined. From the latter results the equilibrium constants for the association of triethylamine with the monomeric alcohol molecules and the effective molecular polarisations and dipole moments of the complexes have been deduced. Association of *n*-butyl alcohol with triethylamine occurs more readily than with pyridine, but that of *tert.*-butyl alcohol occurs less readily. No complex formation between *n*-butyl alcohol and *n*-butyl sulphide, dimethylaniline, or benzotrifluoride, between *tert.*-butyl alcohol and dimethylaniline, or between benzyl alcohol and benzoquinone could be detected by polarisation measurements on dilute solutions. From measurements on benzene solutions at 25° the following dipole moments have been derived: triethylamine 0·80, *n*-butyl sulphide 1·61, and benzotrifluoride 2·56 D.

WHEN this work was begun in 1948, it was known that the apparent molecular polarisations of alcohols in benzene are increased by the presence of small concentrations of pyridine, and that the apparent molecular polarisations of phenols and aromatic amines are higher in dioxan or ether than in benzene. These phenomena were attributable to hydrogen-bond formation between the hydroxylic or amino-hydrogen atoms and the nitrogen atoms of pyridine molecules or oxygen atoms of dioxan or ether molecules. As, therefore, polarisation measurements appeared to present a method of detecting even a weak tendency for intermolecular hydrogen-bonding interaction, it was decided to study the apparent dielectric polarisations of alcohols in benzene solutions in the presence of other compounds the molecules of which contain atoms which may act as electron donors for hydrogen-bond formation, but which contain no hydrogen atoms likely to participate in hydrogen-bonding association. Such compounds include tertiary aliphatic and mixed aliphatic-aromatic amines, ethers, and thio-ethers, and certain ketones and fluorine-containing compounds. Measurements have therefore been made on benzene solutions containing an alcohol together with triethylamine, dimethylaniline, *n*-butyl sulphide, benzoquinone, or benzotrifluoride, and the results compared with those to be expected if the polarisations of the components remained the same as when they are present alone in benzene solution at similar concentrations. Only in the systems containing triethylamine has any detectable enhancement of the polarisation been observed, however, and hence these systems have been studied in greater detail.

For this purpose the dielectric constants, refractive indices, and specific volumes of solutions of triethylamine in benzene and in various mixtures of benzene with *n*- or *tert.*-butyl alcohol have been measured. The results are shown in Table 1, where w_A' and w_B indicate the weight fractions of the alcohol in the solvent mixture and of triethylamine in

the solutions, respectively, and the other symbols have their usual significance. In both systems the apparent molecular polarisation of the triethylamine shows a significant dependence on the concentrations both of the amine itself and of the alcohol, but the corresponding value of the molecular refraction is not increased by the presence of alcohol. From these measurements, together with the results obtained for solutions of the alcohols

TABLE 1. *Polarisation data for triethylamine at 25°.*

Solutions in benzene

$100w_3$	ϵ	v	n_D	p (c.c.)	P_3 (c.c.)	$[R_D]_3$ (c.c.)
0·0000	2·2725	1·14458	1·4980	0·34088	—	—
0·8324	2·2747	1·14663	1·4969	0·34191	47·0	33·6
1·5693	2·2767	1·14842	$1·4959_5$	0·34282	47·0	33·6
2·5213	2·2793	1·15069	1·4948	0·34399	47·0	33·8
3·9361	2·2833	1·15416	1·4930	0·34579	47·1	33·6
5·8653	2·2887	1·15883	1·4906	0·34821	47·1	33·7
0·0000	2·2725	1·14456	1·4979	0·34088	—	—
0·8988	2·2748	1·14675	—	0·34201	47·0	—
1·3291	2·2760	1·14793	—	0·34255	47·2	—
2·2543	2·2783	1·15020	—	0·34368	47·1	—
3·3420	2·2814	1·15282	—	0·34502	47·0	—
3·6921	2·2822	1·15363	—	0·34543	47·0	—
5·5640	2·2871	1·15765	—	0·34756	46·8	—
0·0000	—	1·14456	1·4979	—	—	—
0·7617	—	1·14641	1·4969	—	—	33·4
1·5175	—	1·14833	$1·4959_5$	—	—	33·8
2·4187	—	1·15059	$1·4947_5$	—	—	33·7
3·0877	—	1·15215	1·4940	—	—	33·8
3·8543	—	1·15395	1·4930	—	—	33·7

Solutions in benzene–n-butyl alcohol mixtures

$100w_4'$	$100w_2$	ϵ	v	n_D	p (c.c.)	P_2 (c.c.)	$[R_D]_2$ (c.c.)
1·119	0·0000	2·3172	1·14603	1·4965	0·34967	—	—
	0·5177	2·3221	1·14717	1·4959	0·35091	59·6	33·7
	1·5613	2·3304	1·14957	1·4947	0·35317	58·1	33·9
	2·4764	2·3360	1·15165	$1·4935_5$	0·35485	56·6	33·7
	3·2378	2·3396	1·15362	$1·4925_5$	0·35611	55·5	33·7
	4·2270	2·3437	1·15570	1·4914	0·35750	54·1	33·7
	6·9467	2·3513	1·16213	1·4882	0·36090	51·7	33·7
3·882	0·0000	2·4348	1·14926	1·4931	0·37182	—	—
	0·7725	2·4536	1·15079	1·4923	0·37561	87·3	33·8
	1·3628	2·4658	1·15194	1·4916	0·37810	84·2	33·3
	2·6619	2·4866	1·15463	1·4902	0·38258	78·5	33·4
	3·4780	2·4964	1·15640	1·4894	0·38485	75·5	33·6
	4·7494	2·5087	1·15912	1·4880	0·38786	71·8	33·6
	5·4927	2·5138	1·16070	1·4872	0·38926	69·7	33·6
6·559	0·0000	2·5498	1·15213	1·4899	0·39245	—	—
	0·5638	2·5745	1·15316	1·4892	0·39691	119·8	—
	1·2026	2·5950	1·15437	$1·4886_5$	0·40070	109·1	33·2
	1·8453	2·6157	1·15556	$1·4880_5$	0·40449	105·7	33·4
	2·7335	2·6366	1·15725	$1·4872_5$	0·40847	99·0	33·6
	4·7409	2·6702	1·16127	$1·4852_5$	0·41530	88·5	33·5
	5·9471	2·6848	1·16420	1·4839	0·41868	84·3	33·8
10·486	0·0000	2·7484	1·15634	1·4849	0·42578	—	—
	0·8836	2·7958	1·15779	$1·4842_5$	0·43353	131·8	34·0
	1·7344	2·8344	1·15923	1·4836	0·43987	125·3	33·6
	2·5175	2·8639	1·16060	1·4829	0·44475	119·3	33·5
	3·3977	2·8918	1·16219	1·4820	0·44945	113·6	33·5
	4·5695	2·9212	1·16435	1·4809	0·45455	106·9	33·4
	7·0021	2·9581	1·16897	1·4786	0·46166	94·9	33·4

Solutions in benzene–tert.-butyl alcohol mixtures

1·025	0·0000	2·3101	1·14662	1·4964	0·34853	—	—
	0·9762	2·3141	1·14892	1·4952	0·34997	50·2	33·8
	1·8479	2·3175	1·15098	1·4941	0·35123	50·0	33·7
	2·8360	2·3212	1·15331	1·4929	0·35262	49·9	33·7
	3·9042	2·3249	1·15583	1·4915	0·35408	49·7	33·9
	4·8634	2·3281	1·15810	1·4903	0·35537	49·5	33·5
	5·9631	2·3316	1·16069	1·4891	0·35681	49·3	33·7

TABLE 1. *(Continued.)*

$100w_A'$	$100w_B$	ε	v	n_D	p (c.c.)	P_B (c.c.)	$[R_D]_B$ (c.c.)
Solutions in benzene–tert.-butyl alcohol mixtures							
2·345	0·0000	2·3586	1·14902	1·4941$_5$	0·35816	—	—
	0·8858	2·3635	1·15110	1·4931	0·35970	53·8	33·9
	2·1451	2·3702	1·15395	1·4916	0·36180	53·4	33·7
	2·4187	2·3716	1·15460	1·4913	0·36226	53·4	33·8
	3·5276	2·3764	1·15701	1·4900	0·36389	52·7	33·6
	4·4192	2·3807	1·15915	1·4889$_5$	0·36534	52·7	33·7
	5·6938	2·3856	1·16206	1·4874	0·36714	52·2	33·6
3·723	0·0000	2·4080	1·15149	1·4921	0·36781	—	—
	1·0824	2·4149	1·15399	1·4909	0·36983	56·1	34·1
	1·8890	2·4193	1·15577	1·4900	0·37119	55·4	33·9
	2·6795	2·4237	1·15749	1·4891	0·37252	55·0	33·8
	3·7054	2·4288	1·15976	1·4879	0·37416	54·6	33·7
	4·7975	2·4342	1·16221	1·4867	0·37591	54·3	33·7
	6·0594	2·4398	1·16499	1·4852$_5$	0·37779	53·9	33·7
6·239	0·0000	2·4892	1·15593	1·4887	0·38346	—	—
	0·8406	2·4958	1·15772	1·4878	0·38519	59·6	33·7
	1·7197	2·5025	1·15960	1·4869	0·38696	59·4	33·7
	2·7528	2·5093	1·16179	1·4858	0·38886	58·7	33·7
	3·6618	2·5149	1·16376	1·4849	0·39048	58·2	33·7
	4·9925	2·5224	1·16661	1·4835$_5$	0·39289	57·9	33·7
	6·1538	2·5293	1·16912	1·4822	0·39474	57·3	33·6
7·770	0·0000	2·5415	1·15862	1·4865	0·39327	—	—
	0·8557	2·5494	1·16040	1·4856	0·39520	62·6	33·4
	1·7972	2·5566	1·16236	1·4846	0·39707	61·2	33·5
	2·7325	2·5638	1·16426	1·4836	0·39893	60·8	33·5
	3·5759	2·5694	1·16603	1·4828	0·40048	60·2	33·5
	4·4710	2·5753	1·16787	1·4818	0·40211	59·8	33·4
	6·1120	2·5851	1·17130	1·4801	0·40493	59·1	33·4

in benzene,[1] the apparent molecular polarisations of triethylamine at zero concentration in the alcohol–benzene mixtures, $(P_{B_\infty})_{AS}$, and of the alcohols at zero concentration in various triethylamine–benzene mixtures, $(P_{A_\infty})_{BS}$, have been calculated. These are summarised in Table 2, where α, β, and γ are the limiting values of $d\varepsilon/dw$, dv/dw, and dn^2/dw, respectively, at zero concentration of solute, and $(P_{A_\infty})_S$ and $(P_{B_\infty})_S$ are the molecular polarisations of the solutes at zero concentration in benzene alone.

It has been shown [2] that if two solutes A and B associate to form an unstable compound AB, the molecular polarisation of which, at zero concentration in an inert solvent, is $(P_{AB_\infty})_S$, it should be possible to deduce the values of $(P_{AB_\infty})_S$ and of K, the association constant of the complex, from dielectric-polarisation measurements alone. If the active masses of A, B, and AB can be represented by their concentrations in mole/c.c., and M_B is the molecular weight of B, a plot of $1/\{(P_{A_\infty})_{BS} - (P_{A_\infty})_S\}$ against $M_B v_{BS}/w_B'$ should be linear, with a slope $1/K\Delta P$ and an intercept on the axis for the former of $1/\Delta P$, where $\Delta P = (P_{AB_\infty})_S - (P_{A_\infty})_S - (P_{B_\infty})_S$. The application of this method gives reasonable values for the dipole moments and association constants of the complexes formed by pyridine with *n*- and *tert.*-butyl alcohol and diphenylmethanol.[3] The values for the present systems of the functions which require plotting are shown in the last two columns of Table 2. They also lead to very good straight lines, and the values of the slopes and intercepts obtained by application of the least-squares method, and the quantities derived from them, are shown in Table 3.

These results should apply to the association of triethylamine molecules with monomeric alcohol molecules. On the other hand the values of $(P_{B_\infty})_{AS}$ apply to systems in which the alcohols themselves are strongly associated, a circumstance which must affect the association of the triethylamine with the alcohol. Hence, as was found for the systems

[1] Boud, Cleverdon, Collins, and Smith, *J.*, 1955, 3793.
[2] Few and Smith, *J.*, 1949, 2781.
[3] Cleverdon, Collins, and Smith, preceding paper.

involving pyridine and *n*- or *tert.*-butyl alcohol, the $(P_{B_\infty})_{AB} - (P_{B_\infty})_S$ values are greater than would be expected from the treatment of the systems as solutions of alcohols in triethylamine–benzene mixtures, and hence the plots of $1/\{(P_{B_\infty})_{AB} - (P_{B_\infty})_S\}$ against $M_A v_{AB}/w_A'$ do not superpose upon those for the reverse system, although the results for the *tert.*-butyl alcohol–triethylamine system are much more nearly superposable than those for the *tert.*-butyl alcohol–pyridine system. In each case, however, the divergences are in

TABLE 2. *Summary of polarisation data for butyl alcohol–triethylamine–benzene systems.*

$100w_A'$	α	β	$-\gamma$	$(P_{B_\infty})_{AB}$ (c.c.)	$[R_D]_B$ (c.c.)	$M_A v_{AB}/w_A'$	$\frac{10^4}{(P_{B_\infty})_{AB} - (P_{B_\infty})_S}$
Triethylamine in n*-butyl alcohol–benzene mixtures*							
0·000	0·264	0·244	0·372	47·0	33·8	—	—
1·119	1·005	0·226	0·359	60·5	33·8	7591	741
3·882	2·65	0·196	0·327	91·6	33·8	2194	224
6·559	4·39	0·181	0·301	120·1	33·7	1302	137
10·486	5·82	0·162	0·270	139·7	33·6	817	108
Triethylamine in tert.*-butyl alcohol–benzene mixtures*							
1·025	0·42	0·236	0·360	50·4	33·8	8292	2941
2·345	0·59	0·229	0·352	54·3	33·8	3632	1370
3·723	0·66	0·223	0·336	56·3	33·8	2292	1075
6·239	0·84	0·213	0·321	60·5	33·7	1373	741
7·770	0·91	0·207	0·312	62·4	33·5	1105	649

$100w_B'$	v_{BS}	$(P_{A_\infty})_{BS}$ (c.c.)	$M_B v_{BS}/w_B'$	$\frac{10^4}{(P_{A_\infty})_{BS} - (P_\infty)_S}$
n*-Butyl alcohol in triethylamine–benzene mixtures*				
0·000	1·14458	80·7	—	—
1·000	1·14702	89·7	11,606	1111
2·000	1·14946	95·2	5815	680
3·000	1·15190	99·3	3885	538
4·000	1·15434	102·0	2920	460
5·000	1·15677	104·5	2341	420
6·000	1·15921	106·5	1955	388
tert.*-Butyl alcohol in triethylamine–benzene mixtures*				
0·000	1·14458	80·7	—	—
1·000	1·14702	83·0	11,606	4348
2·000	1·14946	85·0	5815	2326
3·000	1·15190	86·8	3885	1639
4·000	1·15434	88·4	2920	1298
5·000	1·15677	89·9	2341	1087
6·000	1·15921	91·3	1955	943

TABLE 3. *Association constants in benzene solution and dipole moments of complexes of triethylamine with alcohols.*

	$1/K\Delta P$ $\times 10^5$	$1/\Delta P$ $\times 10^4$	K $\times 10^{-1}$	ΔP (c.c.)	$(P_{AB_\infty})_S$ (c.c.)	$[R_D]_{AB}$ (c.c.)	μ_{AB} (D)
n-Butyl alcohol	749	247	330	40	168	56	2·34
tert.-Butyl alcohol	3491	300	86	33	161	57	2·25

the same sense as was observed for the systems formerly studied, and hence support the explanation then offered.

As is to be expected from the relative strengths of the two bases concerned, the value of K for the system *n*-butyl alcohol–triethylamine is appreciably greater than that for the system *n*-butyl alcohol–pyridine (20×10^2), and is very close to that found for the system *n*-heptyl alcohol–trimethylamine by Denyer, Gilchrist, Pegg, Smith, Tomlinson, and Sutton,[4] using a vapour-partition method (35×10^2). With *tert.*-butyl alcohol, on the other hand, association with triethylamine occurs less readily than with pyridine: this may be ascribed to steric effects which are unfavourable to association, since in certain

[4] Denyer, Gilchrist, Pegg, Smith, Tomlinson, and Sutton, *J.*, 1955, 3889.

conformations the methyl groups of the alcohol and of the triethylamine molecule approach one another fairly closely.

If the apparent dipole moments of the complexes are interpreted as the vector sums of the moments of the alcohols (1·69 D) and of triethylamine (0·80 D), they indicate that the dipoles in the alcohols are directed at angles of 43° and 54½° to the axis of the H–O bond in *n*- and *tert.*-butyl alcohol, respectively. These angles differ in the same sense, and by about the same amount, as was inferred from the results for the complexes with pyridine (60° and 72°, respectively). The two sets of results can be reconciled if it is supposed that there is a small contribution to the moment through a redistribution of the electron density in the O–H···N system, as has been suggested by Hulett, Pegg, and Sutton [5] for such association, and also a consequential modification in the remaining bond moments in the molecules. The difference between the results for the triethylamine and pyridine complexes corresponds to an additional moment along the H–O bond axis of 0·18 and 0·25 D in the *n*- and *tert.*-butyl alcohol complexes, respectively.

The results of measurements on the other systems studied are given in Table 4. For the solutions in the mixed solvents the apparent values of the molecular polarisation of the solute (P_2) are compared with the values found for the same concentrations in benzene (P'). Except for the highest concentrations of benzyl alcohol in the benzene–*p*-benzoquinone mixture, the values of P_2 are within experimental error of, or less than, P_2'. It must be inferred, therefore, that there is insufficient complex formation in these systems at the concentrations studied to produce a significant change in the dielectric polarisation. The fact that for solutions of both *n*- and *tert.*-butyl alcohol in benzene–dimethylaniline mixtures the values of P_2 are lower than in benzene itself, and by an almost constant amount in each case, probably arises from a reduction of the effective molecular polarisation of the dimethylaniline through the increase in the dielectric constant of the medium arising from the addition of the butyl alcohol. This view seems to be supported by the fact that the molecular polarisation values for benzotrifluoride in benzene–*n*-butyl alcohol mixtures are almost exactly those to be expected in benzene solutions of the same dielectric constant. Such results give a warning of the care which should be taken in interpreting small changes in dielectric polarisation quantitatively in terms of hydrogen-bonding association when the effective dipole moment of one of the molecular species concerned is strongly dependent on the dielectric constant of the medium. The alcohols and triethylamine studied here do not suffer from this defect, nor does pyridine, which was used in the previous investigation.

The molecular polarisations at zero concentration, molecular refractions, and dipole moments deduced from the measurements on the various components separately in benzene solution are shown in Table 5, together with the corresponding figures for *p*-benzoquinone in carbon tetrachloride solution.

Our values of $P_{2\infty}$ and μ for triethylamine are in good agreement with those of Higasi,[6] but are appreciably lower than those reported by Barclay, Le Fèvre, and Smythe (50·1 c.c. and 0·91 D).[7] This arises from the fact that the latter authors found a considerable departure from linearity in the ε–w_2 plot, leading to a fairly rapid increase in $\Delta\varepsilon/w_2$ with decrease in w_2. We find ε to be sensibly linear with w_2 over the concentration range studied, the slope α being almost identical with the value of $\Delta\varepsilon/w_2$ found by Barclay, Le Fèvre, and Smythe at the highest concentrations they studied. We also find $[R_D]_2$ to be higher than the value (33·1 c.c.) reported by them, and to agree with the value found by Vogel,[8] which is also indicated by our own measurements on the pure liquid.

The dipole moment found for benzotrichloride is close to previous values (2·56,[9] 2·60 D [10]). The mesomeric mechanism suggested by Roberts, Webb, and McElhill [10] to account for the fact that this moment is higher than that of trifluoromethyl*cyclo*hexane

[5] Hulett, Pegg, and Sutton, *J.*, 1955, 3901.
[6] Higasi, *Sci. Pap. Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 211.
[7] Barclay, Le Fèvre, and Smythe, *Trans. Faraday Soc.*, 1950, **46**, 812.
[8] Vogel, *J.*, 1948, 1830.
[9] Freiser, Hobbs, and Gross, *J. Amer. Chem. Soc.*, 1949, **71**, 111.
[10] Roberts, Webb, and Elhill, *ibid.*, 1950, **72**, 408.

TABLE 4. *Polarisation data.*

$100w_2$	ε	v	n_D	P_2 (c.c.)	R_D (c.c.)
n-Butyl sulphide in benzene					
0·0000	2·2725	1·14458	1·4979	—	—
1·1666	2·2924	1·14532	1·4972	99·8	—
1·9566	2·3062	1·14593	1·4967	100·0	46·9
2·5968	2·3173	1·14629	1·4963	99·8	46·8
3·8298	2·3382	1·14713	1·4957	99·6	47·0
5·0269	2·3593	1·14783	1·4949	99·4	46·9
5·4504	2·3668	1·14816	1·4947	99·4	46·9
Benzotrifluoride in benzene					
0·0000	2·2725	1·14458	1·4979	—	—
0·9262	2·3156	1·14198	$1·4972_5$	164·0	31·2
1·3762	2·3359	1·14074	1·4969	162·5	31·0
1·5063	2·3423	1·14039	1·4968	162·5	31·0
2·3891	2·3833	1·13796	1·4961	161·2	30·8
2·6512	2·3950	1·13720	1·4959	160·4	30·8
3·2767	2·4248	1·13545	1·4954	160·0	30·7
4·0261	2·4596	1·13340	$1·4948_5$	159·2	30·9
4·1568	2·4669	1·13299	$1·4947_5$	159·4	30·8
5·4780	2·5295	1·12935	1·4938	157·7	30·9
7·0079	2·6060	1·12482	1·4926	156·8	30·7

$100w_2$	ε	v	n_D	P_2 (c.c.)	R_D (c.c.)
p-Benzoquinone in benzene					
0·0000	2·2725	1·14457	1·4979	—	—
0·5141	2·2752	1·14300	1·4980	37·7	28·5
0·7832	2·2762	1·14220	1·4981	36·7	28·4
0·9020	2·2770	1·14182	1·4981	37·2	28·0
1·0770	2·2778	1·14129	1·4982	37·2	28·7
1·3385	2·2792	1·14042	1·4982	37·0	28·0
1·8685	2·2818	1·13881	1·4984	37·0	28·0
1·9149	2·2820	1·13871	1·4985	37·1	28·7
2·0509	2·2830	1·13827	1·4985	37·3	28·5
2·3884	2·2847	1·13728	1·4985	37·3	28·2
3·2314	2·2889	1·13467	1·4989	37·2	28·4
3·5536	2·2908	1·13362	1·4989	37·3	28·2
5·2114	2·2990	1·12860	1·4995	37·1	28·4
p-Benzoquinone in carbon tetrachloride					
0·0000	2·2252	0·63135	1·4574	—	—
0·4894	2·2301	0·63244	1·4580	38·1	29·4
0·7298	2·2322	0·63295	1·4583	37·5	29·3
1·3577	2·2387	0·63431	1·4590	38·0	29·2

$100w_2$	ε	v	n_D	P_2 (c.c.)	R_D (c.c.)	P_2' (c.c.)
n-Butyl alcohol in benzene + n-butyl sulphide (5·72 wt. %)						
0·0000	2·3716	1·14830	1·4943	—	—	—
0·9129	2·4078	1·14936	1·4934	82·0	—	82·1
1·9075	2·4501	1·15059	1·4920	83·6	22·3	83·4
2·6053	2·4807	1·15134	1·4913	84·1	22·4	83·9
4·0779	2·5448	1·15304	1·4895	84·2	22·3	84·3
4·7938	2·5763	1·15371	1·4889	84·1	22·2	84·2
5·3422	2·6007	1·15427	1·4880	84·0	22·2	84·2
n-Butyl alcohol in benzene + dimethylaniline (6·01 wt. %)						
0·0000	2·4273	1·13894	1·5011	—	—	—
0·9009	2·4606	1·14020	1·5000	78·0	—	82·1
1·7061	2·4937	1·14116	1·4989	80·0	22·3	83·2
2·4613	2·5264	1·14209	1·4977	81·3	21·8	83·8
3·2811	2·5612	1·14318	1·4964	81·7	21·8	84·1
4·4026	2·6115	1·14438	1·4953	82·3	22·0	84·3
5·1695	2·6458	1·14530	$1·4941_5$	82·5	21·8	84·2
tert.-Butyl alcohol in benzene + dimethylaniline (7·60 wt. %)						
0·0000	2·4634	1·13733	1·5022	—	—	—
0·9163	2·4965	1·13922	1·5008	78·2	22·9	80·5
1·7709	2·5247	1·14093	1·4993	76·1	22·3	80·3
2·7839	2·5599	1·14289	1·4979	75·8	22·7	79·6
3·8084	2·5950	1·14480	1·4964	75·3	22·7	78·5
4·4623	2·6172	1·14594	1·4959	74·9	22·6	77·7
5·0029	2·6330	1·14692	1·4957	74·1	22·6	77·2

$100w_2$	ε	v	n_D	P_2 (c.c.)	R_D (c.c.)	P_2' (c.c.)
Benzyl alcohol in benzene + p-benzoquinone (5·43 wt. %)						
0·0000	2·3008	1·12798	1·4994	—	—	—
1·1329	2·3352	1·12601	$1·4998_5$	91·0	32·8	91·4
2·2608	2·3731	1·12411	1·5003	93·3	32·8	93·5
3·5633	2·4199	1·12182	1·5008	95·3	32·7	95·2
5·3419	2·4873	1·11869	1·5017	96·9	32·9	96·3
7·9736	2·5926	1·11407	$1·5024_5$	98·2	32·6	97·0
Benzotrifluoride in benzene + n-butyl alcohol (6·194 wt. %)						
0·0000	2·5511	1·15220	1·4900	—	—	—
0·8089	2·5885	1·14983	$1·4894_5$	154·5	—	164·0
1·2792	2·6107	1·14849	1·4891	154·8	—	162·8
2·0323	2·6453	1·14635	1·4886	153·3	—	161·4
2·8902	2·6858	1·14393	$1·4879_5$	152·9	—	160·3
4·3920	2·7568	1·13957	1·4870	151·1	—	159·2
5·5897	2·8120	1·13613	1·4861	149·3	—	157·6

TABLE 5.

Compound		$10^6\alpha$	$10^6\beta$	$10^6\gamma$	P_∞ (c.c.)	$[R_D]_2$ (c.c.)	μ (D)
Triethylamine	(B)	264	244	−372	47·0	33·8	0·80
n-Butyl sulphide	(B)	1725	66	−178	100·1	46·9	1·61
Benzotrifluoride	(B)	4610	−279	−226	164·4	30·8	2·56
p-Benzoquinone	(B)	508	−306	88	37·3	28·4	—
p-Benzoquinone	(C)	994	219	353	38·0	29·3	—

(B) = Benzene solution; (C) = carbon tetrachloride solution.

would seem to favour the possibility of hydrogen-bonding by the fluorine atoms, but any such association which occurs in the system studied is apparently too weak to be detected by this dilute-solution method.

Our value for the moment of *n*-butyl sulphide is slightly higher than values previously reported (1·57,[11] 1·56 D [12]). This is appreciably greater than the moment of an aliphatic ether (~1·22 D), a fact which supports the view that the association which leads to an increase in polarisation in solutions of alcohols in ethers is not a simple dipole association, since the latter type of association should occur even more strongly with thio-ethers.

Both our $P_{2\infty}$ and $[R_D]$ values for benzoquinone in benzene are appreciably lower than those reported by Le Fèvre and Le Fèvre,[13] but close to those of Hammick, Hampson, and Sutton,[14] as is our $P_{2\infty}$ value for carbon tetrachloride solutions. We find the $[R_D]$ value in the latter solvent to be slightly higher than in benzene, however. As a result, the differences between $P_{2\infty}$ and $[R_D]$, attributable to atom polarisation, are 8·9 and 8·7 c.c. in benzene and carbon tetrachloride, respectively, as compared with Hammick, Hampson, and Sutton's values of 8·83 and 9·59 c.c., respectively, and Coop and Sutton's value of 8·2 c.c. for the vapour.[15]

Experimental

Materials.—Benzene, *n*- and *tert.*-butyl alcohol, benzyl alcohol, and dimethylaniline were purified as described previously.[1,16] Commercial pure triethylamine was kept for some weeks over potassium hydroxide and distilled twice from this reagent, the middle fractions being collected. The product used had n_D^{25} 1·3980, d_4^{25} 0·72350, whence $[R_D] = 33·8$ c.c. *n*-Butyl sulphide, prepared from pure *n*-butyl bromide and sodium sulphide by Bost and Conn's method,[17] had n_D^{25} 1·4505, d_4^{25} 0·8366, $[R_D]$ 47·0 c.c. Pure commercial benzotrifluoride was dried ($CaCl_2$) and fractionally distilled, the sample used having b. p. 102·8°/778 mm., n_D^{25} 1·41215, d_4^{25} 1·18132, $[R_D]$ 30·8 c.c. *p*-Benzoquinone was prepared by oxidising quinol with sodium dichromate and sulphuric acid.[18] It was recrystallised twice from benzene and finally sublimed: it had m. p. 113·6°.

Methods.—The dielectric constants of the solutions, relative to that of pure benzene, were measured with a modified form of the heterodyne-beat apparatus described by Few, Smith, and Witten.[19] The densities were measured with a pyknometer (about 10 c.c. capacity), and the refractive indices with both Pulfrich and Abbé refractometers. All measurements were made at 25°.

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[11] Hunter and Partington, *J.*, 1932, 2812.
[12] Jensen, *Z. anorg. Chem.*, 1935, **225**, 97.
[13] Le Fèvre and Le Fèvre, *J.*, 1935, 1696.
[14] Hammick, Hampson, and Jenkins, *J.*, 1938, 1263.
[15] Coop and Sutton, *J.*, 1938, 1269.
[16] Few and Smith, *J.*, 1949, 753.
[17] Bost and Conn, *Org. Synth.*, 1935, **15**, 72.
[18] Vliet, *ibid.*, 1922, **2**, 85.
[19] Few, Smith, and Witten, *Trans. Faraday Soc.*, 1952, **48**, 211.

868. *The Structure of Molecules and Ions of the Type* $X_2A{\cdot}AX_2$, $X_2A{\cdot}AY_2$, *and* $YXA{\cdot}AXY$.

By P. J. Wheatley.

The structure of molecules and ions of the type $X_2A{\cdot}AX_2$, $X_2A{\cdot}AY_2$, and $YXA{\cdot}AXY$ has been examined in terms of the isoelectronic principle, and an attempt has been made to account for some of the observed regularities. Substances with 12, 24, or 36 electrons prove to be planar. Substances with 14, 26, or 38 electrons are non-planar. Those with 10, 22, or 34 electrons are usually planar, and probably always so in the gas phase, but in the solid strong lattice forces are sometimes sufficient to bring about a twisting of the two halves of the molecule. The observed structures of these simple molecules are used to indicate the general applicability of the isoelectronic principle to more complex molecules.

Numerous substances of the type $X_2A{\cdot}AX_2$, $X_2A{\cdot}AY_2$, and $YXA{\cdot}AXY$ have been studied by physical methods, and their structures elucidated. Some of them have been the subjects of recent doubt or controversy.[1, 2] This paper correlates the known information in terms of the isoelectronic principle. Certain regularities in the shape and size of the molecules can be seen, and an attempt is made to account qualitatively for these observations, and to make some predictions. The fact that, as shown by Walsh,[3] there seem to be no exceptions to the isoelectronic principle when applied to simple molecules, suggests that prediction should not be too hazardous.

Simple Molecules.—In the Table a selection of molecules and ions is listed, together with the length of the central bond where known. The planarity of the molecule is indicated, and also the number of valency electrons. (If X or Y is polyatomic, the shape refers to the six central atoms, and the number of valency electrons is reckoned for these six atoms, counted in terms of the octet theory.) It will be seen that molecules with 10, 22, or 34 electrons, or with 12, 24, or 36 electrons are planar, but that molecules with 14, 26, or 38 electrons are non-planar. This correlation suggests that molecules such as $H_2N{\cdot}NO_2$ and B_2F_4 will be planar, whereas P_2H_4, N_2F_4, and Cl_2O_4, if they can be prepared and studied, will prove to be non-planar.

The central bond in molecules with 12, 24, or 36 electrons has the standard double-bond length. Molecules with 14, 26, or 38 electrons have a central bond length which is equal to, or a little longer than, a typical single bond. However, the molecules with 10, 22, or 34 electrons present a problem. It has long been puzzling that molecules such as oxalic acid should have the central atoms joined by what is apparently, from the length, a single bond. Nevertheless the information in the Table shows that this feature is common to many of the molecules with this number of valency electrons. Indeed, provided that both X and Y have unshared electron pairs, the preferrred π-orbitals seem to belong to each half of the molecule separately, with no conjugation occurring between the two halves. If, however, only one of X or Y had unshared pairs, as in $(CHO)_2$, $(Me{\cdot}CO)_2$, and $(MeC{:}NOH)_2$, then the central bond is shortened, and a π-orbital involving both halves of the molecule seems to be involved. There seem to be no exceptions to this rule [although $(COCl)_2$ might bear reinvestigation], and it suggests an interesting way of regarding oxalic acid and its isoelectronic analogues. In such molecules the unshared pairs seem to be affecting only the A–X and A–Y bonds and not the A–A bond. Thus, for a discussion of the length of the A–A bond, it seems legitimate to ignore the unshared electrons and concentrate on the σ-bond skeleton. It must be emphasised that this rather radical procedure can only be adopted if both X and Y have unshared electron pairs; it then justifies itself because the results which follow seem to agree with experiment.

In order to consider the σ-bond skeleton of these molecules, it is convenient to start with

[1] Atoji, Lipscomb, and Wheatley, *J. Chem. Phys.*, 1955, **23**, 1176.
[2] Gray and Yoffe, *Quart. Rev.*, 1955, **9**, 385.
[3] Walsh, *J.*, 1953, 2260, 2266, 2288, 2296, 2301, 2306, 2318, 2321, 2325, 2330.

ethylene [4, 5] since it is probably the most extensively studied of these molecules. Ethylene has 12 valency electrons in orbitals which may be designated, in probable order of increasing energy, as a_{1g}, b_{1u}, a_{1g}, b_{2u}, b_{2g}, and b_{3u}.[5] The order of the five lowest orbitals is not particularly relevant to the present discussion, but it is imperative that the highest occupied

Molecules and ions of the type $X_2A{\cdot}AX_2$, $X_2A{\cdot}AY_2$, *and* $YXA{\cdot}AXY$ *with the number of valency electrons and the* A–A *bond length* (Å).

Planar molecules.

Electrons	Compound	Bond length	Ref.	Electrons	Compound	Bond length	Ref.	Electrons	Compound	Bond length	Ref.
10	B_2H_4	—	—	34	$(CO{\cdot}NH_2)_2$	1·542	*e*	12	C_2H_4	1·34	*m*, *n*
				,,	$(CO_2Me)_2$	1·53	*f*	,,	,,	1·353	
22	$(CHO)_2$	1·47	*a*	,,	α-$(CO_2H)_2$	1·560	*g*				
				,,	β-$(CO_2H)_2$	1·57	*h*	24	$H_2N{\cdot}NO_2$	—	—
34	B_2F_4	—	—	,,	$(CO_2H)_2,2H_2O$	1·529	*i*	,,	$H_2C{:}CF_2$	1·311	*o*
,,	B_2Cl_4	1·75	1	,,	$(CO_2NH_4)_2,H_2O$ *	1·56	*j*	,,	$H_2C{:}CCl_2$	—	—
,,	N_2O_4	1·64	*b*	,,	$(COCl)_2$	1·50	*r*	,,	*cis*-(:CHMe)$_2$	1·38	*p*
,,	$C_2O_4^{2-}$	1·54	*c*	,,	$(COMe)_2$	1·47	*a*	,,	*trans*-(:CHMe)$_2$	1·40	*p*
,,	$(CS{\cdot}NH_2)_2$	1·544	*d*	,,	$(MeC{:}NOH)_2$	1·44	*l*				
	,,	1·534	*d*					36	C_2F_4	1·313	*o*
								,,	C_2Cl_4	1·30	*q*
								,,	$Me_2N{\cdot}NO_2$	1·30	*r*
								,,	,,	1·26	*s*

Non-planar molecules.

Electrons	Compound	Bond length	Ref.	Electrons	Compound	Bond length	Ref.	Electrons	Compound	Bond length	Ref.
14	N_2H_4	1·46	*t*, *u*	26	$Me_2N{\cdot}NH_2$	1·45	*v*	38	N_2F_4	—	—
,,	,,	1·47	,,	,,	$(NHMe)_2$	1·45	*v*	,,	Cl_2O_4	—	—
,,	P_2H_4	—	—					,,	$S_2O_4^{2-}$	2·389	*w*

* The oxalate ion in $(CO_2NH_4)_2,H_2O$ is non-planar.

There is experimental evidence for the shape of the molecule or ion only when a literature reference is cited.

[a] LuValle and Schomaker, *J. Amer. Chem. Soc.*, 1939, **61**, 3520. [b] Broadley and Robertson, *Nature*, 1949, **164**, 915. [c] Jeffrey and Parry, *J. Amer. Chem. Soc.*, 1954, **76**, 5283. [d] Long, Markey, and Wheatley, *Acta Cryst.*, 1954, **7**, 140. [e] Ayerst and Duke, *ibid.*, p. 588. [f] Dougill and Jeffrey, *ibid.*, 1953, **6**, 831. [g] Cox, Dougill, and Jeffrey, *J.*, 1952, 4854. [h] Hendricks, *Z. Krist.*, 1935, **91**, 48. [i] Ahmed and Cruickshank, *Acta Cryst.*, 1953, **6**, 385. [j] Jeffrey and Parry, *J.*, 1952, 4864. [k] Merritt and Lanterman, *Acta Cryst.*, 1952, **5**, 811. [l] Pauling and Brockway, *J. Amer. Chem. Soc.*, 1937, **59**, 1223. [m] Gallaway and Barker, *J. Chem. Phys.*, 1942, **10**, 88. [n] Karle and Karle, *ibid.*, 1950, **18**, 963. [o] Brockway and Cross, *J. Amer. Chem. Soc.*, 1936, **58**, 2407. [p] Karle and Karle, *J. Chem. Phys.*, 1952, **20**, 63. [q] Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46. [r] Costain and Cox, *Nature*, 1947, **160**, 826. [s] Collin and Lipscomb, *Acta Cryst.*, 1951, **4**, 10. [t] Giguere and Schomaker, *J. Amer. Chem. Soc.*, 1943, 2025. [u] Beamer, *ibid.*, 1948, **70**, 2979. [v] Dunitz, *ibid.*, 1956, **78**, 878.

orbital should be the b_{3u} or π orbital, and it is generally accepted that this is so. Above the b_{3u} or π orbital lies the b_{2g} or $\bar{\pi}$ orbital, which is not occupied in normal ethylene, but is occupied in hydrazine. A simple picture shows that the electrons in the π orbital have lowest energy when the two halves of the molecule lie in the same plane, whereas those in the $\bar{\pi}$ orbital have lowest energy when the two halves have their planes at right-angles. It is understandable, therefore,[5] that ethylene should be planar in the ground state, but possibly twisted in the first excited state, when one electron has been raised from the π to the $\bar{\pi}$ orbital, and that hydrazine should be twisted in the ground state. These remarks will be applicable to those analogues of ethylene which contain **24** and **36** electrons, and also to those analogues of hydrazine which contain **26** and **38**.

In molecules with two electrons less than ethylene the two electrons dispensed with are those from the π orbital, and this leaves a single σ bond joining the two halves of the molecule. The same will be true of molecules containing 22 and **34** electrons, provided that the unshared pairs on X and Y can be ignored.

The planarity of ethylene is well understood, but the planarity of molecules with **10**, **22**, or **34** electrons is by no means obvious, unless only one of X and Y have unshared pairs,

[4] Crawford, Lancaster, and Inskeep, *J. Chem. Phys.*, 1953, **21**, 678.
[5] Walsh, *J.*, 1953, 2325.

when conjugation between the two halves would tend to stabilise the planar form. It has been suggested that in oxalic acid electrostatic attraction between the hydroxyl and carbonyl oxygen atoms causes the planar form to be preferred,[6] but this seems implausible because the planarity persists when oxygen atoms are replaced by NH_2, Cl, and S. Of the orbitals that have been considered, b_{1u}, b_{3g}, and b_{2g} will tend to stabilise the twisted form of the molecule, whereas a_{1g}, a_{1g}, b_{2u}, and b_{3u} favour the planar configuration. Thus, of the six orbitals used in ethylene, four favour the planar configuration and two the twisted form, so that, if all orbitals are assigned the same weight, a planar C_2H_4 molecule is to be expected. Similarly, in the molecules with 10, 22, and 34 electrons, three of the orbitals favour a planar, and two the twisted, form so that the balance still favours planar structures. Unfortunately a similar argument applied to hydrazine and its analogues results in four orbitals favouring the planar and three the twisted form, yet the molecules are non-planar. It would be valuable to have sufficient information to construct correlation diagrams for molecules with 10, 22, or 34 electrons giving the energy of the orbitals as a function of the dihedral angle, because it does appear that an explanation for their planarity lies in the relative energy levels in the planar and twisted forms of the five orbitals occupied by the σ electrons.

If this statement is valid, some conclusions may be drawn about the spectra of these molecules, which may serve to test some of the assumptions made here. In passing from molecules with 12, 24, or 36 electrons to those with 10, 22, or 34 electrons, the two electrons which strongly favour the planar form have been eliminated. Thus molecules containing 10, 22, or 34 electrons will be " only just " planar. Relatively small forces might suffice to twist the molecule, and this is confirmed by the shape of the oxalate ion in ammonium oxalate hemihydrate, where the extensive hydrogen bonding seems able to twist the ion so that the dihedral angle is 28°. However, it appears from the Table that more than van der Waals forces are necessary to cause the distortion. Nevertheless, compared with that in ethylene, there will be only a small force constant opposing twisting in molecules with 10, 22, and 34 electrons leading, after allowance for mass factors, to a much lower value of the twisting frequency. Unfortunately this frequency is inactive in both the Raman and infra-red spectra of A_2X_4 molecules, but accurate values of the other frequencies are becoming available,[7, 8] and it is possible that the twisting frequencies will be deduced indirectly.

Even greater differences should be observable in the electronic spectra. In molecules with 12, 24, or 36 electrons an electron is first excited from the π to the $\bar{\pi}$ orbital, favouring a twisting of the molecule and a lowering of the twisting frequency. In molecules with 10, 22, or 34 electrons an electron will be excited to the π orbital, making the molecule much more firmly planar in the first excited state, and considerably increasing the twisting frequency.

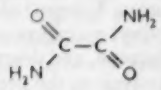
More Complex Molecules.—Whether or not this interpretation is valid, there remains the large body of information in the Table which can be used to correlate and predict the structures of less symmetrical and more complex molecules. It will be noticed that we have been considering arithmetical series, with a difference of twelve; in less symmetrical molecules where, for instance, H with one valency electron might replace CH_3 with seven, the difference will be reduced to six, so that molecules with 12, 18, 24, 30, or 36 electrons will be planar. The number of applications that can be made is very large, and this discussion will be restricted mainly to some of those cases which have been confirmed experimentally.

Formamide has 18 electrons so that all the atoms should lie in one plane.[9] Oxamide has previously been regarded as (I). However, the system of atoms (II) is part of the oxamide molecule and has 24 electrons. Thus this part of the molecule must also be planar, and it follows that all the atoms in the oxamide molecule must lie in one plane. The same will be true of dithio-oxamide. Urea can be regarded as (III), which again has 24 electrons.[10]

[6] Jeffrey and Parry, *Nature*, 1952, **169**, 1105.
[7] Ito and Bernstein, *Canad. J. Chem.*, 1956, **34**, 170.
[8] Snyder, Hisatsune, and Crawford: Presented at the Symposium on Molecular Structure and Spectroscopy, Ohio State University, June 1956.
[9] Ladell and Post, *Acta Cryst.*, 1954, **7**, 559.
[10] Vaughan and Donohue, *Acta Cryst.*, 1952, **5**, 530.

Since each half of the molecule can be regarded separately, again the whole molecule must be planar. Guanidine and thiourea [11] can be similarly treated. The same argument can be applied to the amide grouping (II) in general, and there are several structures showing the planarity of this basic unit which plays such a large part in more complex molecules.[12] Similarly all the atoms except the methylene hydrogen atoms in ethylenethiourea [13] (IV) must be in one plane. The group of atoms shown in (V) is part of the benzene molecule, and again has 24 electrons. By taking the carbon atoms in pairs, it follows that the whole molecule is planar. Similarly dihydropyrazine (VI) will be planar. On the other hand, in 1 : 4-dithiin (VII) [14] a similar argument can only be applied to each half of the molecule. It follows that the molecule must have the boat form, but nothing can be said from these considerations about the planarity of the whole molecule. The same is true for the higher analogues such as thianthrene,[15] whereas naphthalene and anthracene must be totally planar.

Half of the *p*-dinitrobenzene molecule is shown in (VIII), and this has 34 electrons; the whole molecule should therefore be planar. However, this system is analogous to the oxalate ion, the C–N length being typically single with a value of 1·48 Å, and, as in ammonium oxalate, the lattice forces appear to be sufficient, even without the presence of hydrogen bonds, to cause a slight twisting so that the angle [16] between the planes of the nitro-group and the benzene ring is $9\frac{1}{2}°$.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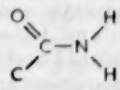
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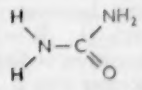
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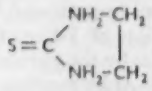
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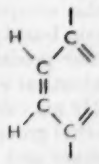
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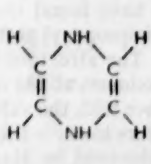
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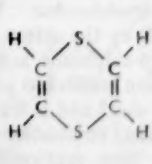
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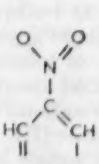
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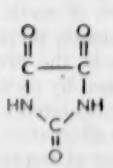
(IX)

Finally parabanic acid (IX) is a molecule which illustrates well some of the points mentioned here.[17] The system of six atoms containing the two linked carbon atoms has 34 electrons, and the C–C bond has the typical single-bond value [18] of 1·541 Å. The other systems of six atoms have 30 electrons, so that the whole molecule is planar. It is also interesting to note that, whereas molecules of the type $YXA{\cdot}AXY$ adopt the *trans*-form, in parabanic acid the carboxyl groups must necessarily be *cis* to each other. The molecule is therefore under a form of constraint, which is insufficient, however, to remove the planarity.

I acknowledge valuable discussions with Professor A. D. Walsh and many of my colleagues at Leeds.

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[*Received, June 1st,* 1956.]

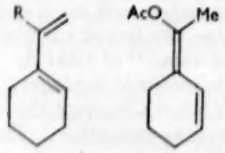
[11] Wyckoff, *Z. Krist.*, 1932, **81**, 386.
[12] Pauling and Corey, *Proc. Nat. Acad. Sci.*, 1951, **37**, 235.
[13] Wheatley, *Acta Cryst.*, 1953, **6**, 369.
[14] Howell, Curtis, and Lipscomb, *Acta Cryst.*, 1954, **7**, 498.
[15] Lynton and Cox, *J.*, 1956, in the press.
[16] Abrahams, *Acta Cryst.*, 1950, **3**, 194.
[17] Hughes, *Ann. Rev. Phys. Chem.*, 1955, **6**, 271.
[18] Davies and Blum, *Acta Cryst.*, 1955, **8**, 129.

869. *Reduced Cyclic Compounds. Part II.* The Synthesis of 1-1′-Acetoxyvinylcyclohexene and its Reactions with Some Dienophils.†*

By M. F. Ansell and G. T. Brooks.

The preparation of 1-1′-acetoxyvinyl*cyclo*hexene and its conversion into 4-acetoxy-Δ^4-octahydronaphthalene-1 : 2-dicarboxylic anhydride, and the phenanthrene derivatives (VIII; R = OAc) and (XI), and related compounds are described.

The use of the Diels–Alder reaction in the synthesis of reduced cyclic systems related to the steroids has been extensively studied,[1] and it has been shown [2] that by the use of an alkoxybutadiene, *e.g.*, 3-methoxybuta-1 : 3-diene, it is possible to prepare cyclic compounds containing a potential carbonyl group. Robinson and Acheson,[3] and Newman and McPherson,[4] have pointed out that by the use of a suitable oxygenated diene the Diels–Alder reaction might be used as a route to 11-keto-steroids. A suitable model compound for such an investigation is a 1′-acyloxy- (I; R = R·CO·O) or 1′-alkoxy-derivative (I; R = R′O) of 1-vinyl*cyclo*hexene. At the commencement of this work no compound of this type was known, although the use of 1-vinyl*cyclo*hexene in the Diels–Alder reaction had been investigated.[5,6] Later, however, Favorskaya and Fedorova [7] reported the preparation of 1-1′-methoxyvinyl- (I; R = OMe) and 1-1′-ethoxyvinyl-*cyclo*hexene (I; R = OEt) by the pyrolysis of the corresponding ketals of 1-acetyl*cyclo*hexene, and described the Diels–Alder reaction of the former with 2 : 5-xyloquinone and hydrolysis of the product (the structure of which was not determined) to a tricyclic triketone. Nazarov [8] has described the preparation of 1-1′-acetoxyvinyl*cyclo*hexene (I; R = OAc) (in 37% yield) by the addition of acetic acid to 1-ethynyl*cyclo*hexene. We have found that this compound is conveniently prepared (in 84% yield) by the action of *iso*propenyl acetate on 1-acetyl*cyclo*hexene in the presence of toluene-*p*-sulphonic acid. The structure of our product was confirmed by its ultraviolet absorption which has a maximum at 232 mμ identical with the value calculated from Woodward's rules [9] and at variance with the value 242 mμ calculated for the alternative structure (II). That enolisation occurs towards the methyl group in the presence of *iso*propenyl acetate has been previously observed by Hagemeyer and Hull [10] and is exemplified by the formation [11] of $\Delta^{16:20}$-enol acetates from Δ^{16}-20-keto-steroids.



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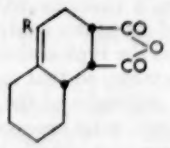

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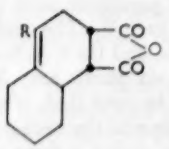


(IV)

The reaction of the acetoxy-diene (I; R = OAc) with maleic anhydride yielded 4-acetoxy-Δ^4-octahydronaphthalene-1 : 2-dicarboxylic anhydride (III; R = OAc) (m. p. 84—86°). Catalytic dehydrogenation was unsuccessful, but dehydrogenation by the

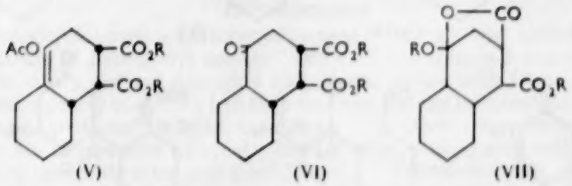
* Part I, *J.*, 1956, 1238.
† Preliminary communication, *Chem. and Ind.*, 1955, 916.

[1] For reviews see : Norton, *Chem. Rev.*, 1942, **31**, 319; Butz, "Organic Reactions," Vol. V, p. 136.
[2] Sarett, Lukes, Poos, Robinson, Beyler, Vandegrift, and Arth, *J. Amer. Chem. Soc.*, 1952, **74**, 1393.
[3] Robinson and Acheson, *J.*, 1952, 1128.
[4] Newman and McPherson, *J. Org. Chem.*, 1954, **19**, 1717.
[5] Cook and Lawrence, *J.*, 1938, 58.
[6] Robins and Walker, *J.*, 1952, 642, 1610.
[7] Favorskaya and Fedorova, *Z. obshchei Khim.*, 1954, **24**, 242; 1955, **25**, 1477.
[8] Nazarov, Kucherov, Andreyev, and Segal, *Doklady Akad. Nauk S.S.S.R.*, 1955, **104**, 729.
[9] Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72.
[10] Hagemeyer and Hull, *Ind. Eng. Chem.*, 1949, **41**, 2920.
[11] Moffett and Weisblat, *J. Amer. Chem. Soc.*, 1952, **74**, 2183.

exhaustive bromination method [12] gave 4-acetoxynaphthalene-1 : 2-dicarboxylic anhydride which has an ultraviolet absorption spectrum almost identical with that of naphthalene-1 : 2-dicarboxylic anhydride.

On the basis of Alder and Stein's rules [13] and the mild conditions under which it was prepared we consider that the anydride (III; R = OAc) has the *syn-cis*-configuration shown.* Under more drastic conditions (eight hours in boiling benzene) Nazarov [8] obtained a liquid product to which he assigns the *anti-cis*-structure (IV; R = OAc). In support of the above assignments of configuration it is relevant that similar results have been obtained in the reaction between 1-vinyl*cyclo*hexene and maleic anhydride. Thus, whereas Cook and Lawrence [5] reported the formation of only the solid *syn-cis*-anhydride (III; R = H) when the reaction occurred in a small amount of solvent at room temperature, Nazarov *et al.*[15] found that allowing the exothermic reaction to proceed in the absence of a solvent gave a liquid product together with the crystalline product. Even when the reaction was allowed to proceed at 2—3° for a long period in benzene solution the *syn-cis*-product (55% yield) was accompanied by a liquid containing the *anti-cis*-anhydride (? liquid) (III; R = H). The latter is also formed when the *syn-cis*-anhydride is heated. Thus mild conditions favour the formation of the *syn-cis*-anhydride (III; R = H).

Treatment of the acetoxy-anhydride (III; R = AcO) with 2 : 4-dinitrophenylhydrazine in acidic ethanol gave the 2 : 4-dinitrophenylhydrazone of a half ester of decahydro-4-oxonaphthalene-1 : 2-dicarboxylic acid (VI; R = H), thus establishing the presence of the potential carbonyl group in the original adduct. Hydrolysis of the acetoxy-anhydride (III; R = OAc) with boiling water gave the acid (V; R = H), the melting point of which depended on the rate of heating, perhaps owing to anhydride formation or lactonisation :



(V) (VI) (VII)

on treatment with diazomethane it yielded the sharply melting methyl ester (V; R = Me). Acid or alkaline hydrolysis of the acetoxy-acid (V; R = H) or -anhydride (III; R = AcO) gave decahydro-4-oxonaphthalene-1 : 2-dicarboxylic acid (VI; R = H), whose melting point is variable owing to hydration. Its infrared absorption has an asymmetric maximum at 1703 cm.$^{-1}$ (C=O stretching region), which together with the absence of absorption in the lactonic-carbonyl region (1740—1800 cm.$^{-1}$) indicates that it does not exist in a lactonic form, *e.g.*, (VII; R = H). With diazomethane it gave the sharply melting methyl ester (VI; R = Me) and not the *pseudo*-ester (VII; R = Me), as is shown by its infrared absorption spectrum in which the maxima due to the methoxy-carbonyl and the keto-carbonyl group are just resolved (1730 and 1705 cm.$^{-1}$). The same ester (VI; R = Me), together with a half ester, was also obtained directly from the acetoxy-anhydride (III; R = OAc) by treatment with methanol in the presence of sulphuric acid. This keto-ester readily formed a 2 : 4-dinitrophenylhydrazone. The same compound was also formed, although more slowly, from the acetoxy-ester (V; R = Me).

Conversion of the acetoxy-anhydride (III; R = OAc) into the keto-acid (VI; R = H) or the keto-ester (VI; R = Me) introduces a new centre of asymmetry. If this occurs to give the more stable *trans*-ring junction, as in α-decalone, and no isomerisation occurs at the

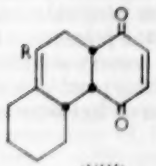
* The dots indicate that hydrogen atoms so denoted are on the side of the carbon skeleton nearer to the reader.[14]

[12] Alder and Schmitz, *Annalen*, 1949, **565**, 123.
[13] Alder and Stein, *Angew. Chem.*, 1937, **50**, 510.
[14] Linstead, *Chem. and Ind.*, 1937, **56**, 510; Linstead and Walpole, *J.*, 1939, 842.
[15] Nazarov, Kucherov, and Andreyev, *Doklady Akad. Nauk S.S.S.R.*, 1955, **102**, 751.

other centres of asymmetry, then the configurations of these compounds are those indicated. Throughout this series of related compounds no evidence was obtained of stereochemical inhomogeneity.

The acetoxy-diene (I; R = AcO) reacted with benzoquinone, in benzene under mild conditions, to give 9-acetoxy-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene (VIII; R = AcO), whose ultraviolet absorption spectrum resembled that of $\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene,[6] and, like the latter, it is sensitive to alkali. Its structure was confirmed by reduction with lithium aluminium hydride (two treatments were necessary [16]) followed by dehydration, and dehydrogenation, to yield phenanthrene.

Application of Alder and Stein's rules to the configuration of this compound (VIII; R = AcO) suggests, in view of the mild conditions under which it is formed, that it has the *syn-cis*-configuration as indicated, comparable with that of the adduct (VIII; R = H) obtained from 1-vinyl*cyclo*hexene and benzoquinone.[6] It is not certain whether these rules are applicable to the adduct (VIII; R = AcO) as in some slow diene reactions of this type the *cis*-compound initially formed may undergo easy stereoisomerisation.[17] Moreover, Nazarov [8] has prepared by the same route, but under more drastic conditions (boiling benzene for 7 hr.), an adduct to which he assigns the *anti-cis*-configuration (IX). On the basis of its melting point, however, this compound appears to be identical with ours.



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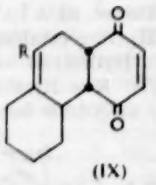

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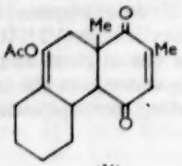
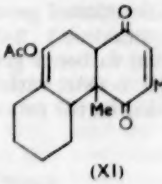
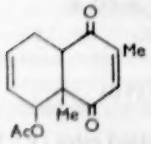


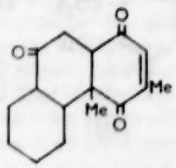
(X)



(XI)



(XII)



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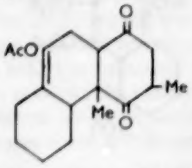
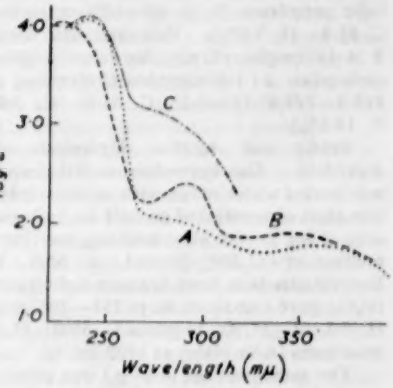


(XIV)

The reaction between 2 : 6-xyloquinone and 1-1'-acetoxyvinyl*cyclo*hexene yielded a homogeneous product which was shown, by degradation to 3-methylphenanthrene, to be 9-acetoxy-$\Delta^{2:9(14)}$-decahydro-3 : 12-dimethyl-1 : 4-dioxophenanthrene (XI) and not the 2 : 11-dimethyl compound (X). An authentic sample of 3-methylphenanthrene was synthesised by a Bogert–Cook synthesis: 4-methyl-1-phenethyl*cyclo*hexanol, from phenethylmagnesium bromide and 4-methyl*cyclo*hexanone, was cyclised with 85% sulphuric acid to 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-3-methylphenanthrene which was then dehydrogenated with selenium. In view of the foregoing discussion and the conditions of formation of the adduct (XI) (21 hours in boiling ethanol or benzene), the use of Alder and Stein's rules to predict the stereochemistry of the product may not be justified. Its ultraviolet spectrum (*cyclo*hexane) shows a general similarity to that of 9-acetoxy-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene with a bathochromic shift of the main maximum to 240 mμ (log ε 4·07). This is in good agreement with main maximum (242 mμ; log ε 4·05) (in *cyclo*hexane) recorded by Stein [18] for 5-acetoxy-$\Delta^{2:6}$-hexahydro-2 : 10-dimethyl-1 : 4-dioxonaphthalene (XII), an ene-dione of the same substitution type. Hydrolysis of the adduct (XI) with aqueous-methanolic sulphuric acid gave Δ^{2}-dodecahydro-3 : 12-dimethyl-1 : 4 : 9-trioxophenanthrene (XIII). The ultraviolet absorption spectrum of the

[16] Cf. Dauben and Eastham, *J. Amer. Chem. Soc.*, 1953, **75**, 1718.
[17] Lukes, Poos, and Sarett, *ibid.*, 1952, **74**, 1402.
[18] Stein and Casini, *Gazzetta*, 1955, **85**, 1411.

latter has a single maximum at 241 mμ corresponding to the ene-dione system; the presence of the isolated carbonyl group is indicated by an increase in the intensity of the shoulder in the spectrum to log ε 3·16 (270 mμ) from that of log ε 2·07 (274—275 mμ) in the parent adduct (XI) (see diagram). Reduction of the adduct (XI) with zinc dust in glacial acetic



Absorption spectra of (A) compound (XI) *(in cyclohexane), (B) compound* (VIII; R = OAc) *(in ethanol), and (C) compound* (XIII) *(in cyclohexane).*

acid at room temperature saturated the conjugated double bond, to yield 9-acetoxy-$\Delta^{9(14)}$-dodecahydro-3 : 12-dimethyl-1 : 4-dioxophenanthrene (XIV).

Experimental

1-1′-Acetoxyvinylcyclohexene.—1-Acetylcyclohexene [19] (62 g.) was added during 15 min. to a boiling mixture of *iso*propenyl acetate (1050 c.c.) and toluene-*p*-sulphonic acid (9·5 g.). The mixture was slowly distilled through a 36″ column packed with Dixon gauzes. After 4½ hr. the theoretical quantity of acetone had been removed and the temperature slowly rose to 97°. Slow distillation was continued for 36 hr. and 650 c.c. of distillate were collected. After cooling, the dark residue was diluted with an equal volume of ether, washed with 10% sodium hydrogen carbonate solution, then with water, and dried (Na_2SO_4). Volatile material, b. p. <40°/15 mm., was removed and the residue distilled from quinol (1·5 g.), to yield after a small fore-run 1-1′-acetoxyvinylcyclohexene (69·5 g., 83·7%) b. p. 66—71°/1 mm., n_D^{20} 1·4980. A redistilled sample had b. p. 66°/0·7 mm., n_D^{20} 1·4990 (Found: C, 72·0; H, 8·5. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·5%). Nazarov [9] records b. p. 99—100°/10 mm., n_D^{20} 1·4972. This material became viscous on exposure to air and was stored in sealed bottles over quinol. On treatment with 2 : 4-dinitrophenylhydrazine sulphate in alcohol it slowly yielded 1-acetylcyclohexene 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 199—200°.

4-Acetoxy-Δ^4-octahydronaphthalene-1 : 2-dicarboxylic Anhydride.—A warm solution of redistilled maleic anhydride (2·8 g., 0·029 mole) in dry thiophen-free benzene (30 c.c.) was added to a solution of 1-1′-acetoxyvinylcyclohexene (5 g., 0·03 mole) in the same solvent (30 c.c.). The mixture developed a transient yellow colour. After 3 days at room temperature the mixture was heated under reflux for 1 hr. Removal of the solvent under reduced pressure left a viscous liquid that solidified on shaking. After being washed with a little ether the crude *4-acetoxy-Δ^4-octahydronaphthalene-1 : 2-dicarboxylic anhydride* (6 g., 80%), m. p. 80—85°, was recrystallised twice from ether to give the pure compound (5 g., 67%) as prisms, m. p. 84—86° (Found: C, 63·5; H, 6·2. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). It was unsaturated towards bromine in carbon tetrachloride and neutralised three equivs. of sodium hydroxide on hydrolysis. Treatment with an alcoholic sulphuric acid solution of 2 : 4-dinitrophenylhydrazine gave *ethyl hydrogen 4-oxodecahydronaphthalene-1 : 2-dicarboxylate 2 : 4-dinitrophenylhydrazone*, orange-yellow plates (from alcohol), m. p. 126° (decomp. with resolidification) (Found: C, 53·0; H, 5·8; N, 12·6. $C_{20}H_{24}O_8N_4$ requires C, 53·6; H, 5·4; N, 12·5%).

Neutral Hydrolysis of 4-Acetoxy-Δ^4-octahydronaphthalene-1 : 2-dicarboxylic Anhydride.—The above anhydride (0·5 g.) was boiled with water until dissolved and for a further 30 min. The filtered solution, on cooling, deposited *4-acetoxy-Δ^4-octahydronaphthalene-1 : 2-dicarboxylic acid*

[19] Royals and Henry, *J. Org. Chem.*, 1950, **15**, 1147.

(0·5 g.) as needles, m. p. 190—202° (Found : C, 60·1; H, 6·9. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). Recrystallisation from water or acetone–light petroleum mixtures did not improve the m. p. which depended on heating conditions and the initial bath-temperature. The acid neutralised three equivs. of sodium hydroxide on hydrolysis. Treatment of the acid with diazomethane in chloroform gave the *dimethyl ester*, m. p. 98—98·5° after recrystallisation from light petroleum (b. p. 40—60°) or methanol (Found : C, 61·8; H, 7·3. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·2%). This ester with a warm aqueous-methanolic hydrochloric acid solution of 2 : 4-dinitrophenylhydrazine slowly gave the *dimethyl decahydro-4-oxonaphthalene*-1 : 2-*dicarboxylate* 2 : 4-*dinitrophenylhydrazone*, golden-yellow plates (from methyl acetate), m. p. 222·5—223·5° (Found : C, 54·0; H, 5·6; N, 12·9. $C_{20}H_{24}O_8N_4$ requires C, 53·6; H, 5·4; N, 12·5%).

Acidic and Alkaline Hydrolysis of 4-*Acetoxy*-Δ^4-*octahydronaphthalene*-1 : 2-*dicarboxylic Anhydride. Decahydro*-4-*oxonaphthalene*-1 : 2-*dicarboxylic Acid.*—The above anhydride (0·4 g.) was heated under reflux with aqueous 0·1N-sodium hydroxide (20 c.c.) for 15 min. The solution was then concentrated to half its bulk under reduced pressure and acidified, to yield the *keto-acid* (0·3 g.). On slow heating, melting (at 157°) was attended by resolidification and final melting at *ca.* 200° (Found : C, 55·9; H, 7·6. $C_{12}H_{16}O_5,H_2O$ requires C, 55·8; H, 7·0%). Recrystallisation from acetone–light petroleum (b. p. 60—80°) followed by prolonged drying (P_2O_5) gave a product, m. p. 191—195° (rapid heating from room temperature) (Found : C, 57·7; H, 7·1. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%). The infrared spectrum had an asymmetric maximum (KBr plate) at 1703 cm.$^{-1}$.

The same product (0·27 g.) was obtained by heating the anhydride (0·4 g.) or 4-acetoxy-Δ^4-octahydronaphthalene-1 : 2-dicarboxylic acid with 0·2N-sulphuric acid (25 c.c.) for 2 hr. All samples, with diazomethane, gave a *dimethyl ester*, m. p. 74—75° (Found : C, 62·9; H, 7·7. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5%), whose infrared spectrum had peaks (in CS_2) at 1206, 1705, and 1730 cm.$^{-1}$ (double peak). This ester rapidly gave the 2 : 4-dinitrophenylhydrazone of decahydrodimethyl-4-oxonaphthalene-1 : 2-dicarboxylate (m. p. and mixed m. p. 222·5—223·5°) under conditions described above.

Alcoholysis of 4-*Acetoxy*-Δ^4-*octahydronaphthalene*-1 : 2-*dicarboxylic Anhydride.*—The above anhydride (6·5 g.) was heated in methanol (125 c.c.) and concentrated sulphuric acid (5 g.) for 42 hr. After removal of half the solvent the residue was diluted with an equal volume of ether, washed with 10% sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). Removal of the ether left dimethyl decahydro-4-oxonaphthalene-1 : 2-dicarboxylate (3·9 g.), m. p. 73°. Recrystallisation from light petroleum (b. p. 60—80°) gave the pure diester, m. p. 74—75°. The above alkaline extract was made acid and extracted with ether, and the ethereal extract washed with water and dried ($MgSO_4$). Removal of the ether left *methyl hydrogen decahydro*-4-*oxonaphthalene*-1 : 2-*dicarboxylic acid* (2·8 g.), m. p. 137—143°. Recrystallisation from benzene gave needles, m. p. 145—146° (Found : C, 61·6; H, 7·3. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·2%). It was converted into the diester (m. p. and mixed m. p. 72—73°) by diazomethane in chloroform.

Dehydrogenation of 4-*Acetoxy*-Δ^4-*octahydronaphthalene*-1 : 2-*dicarboxylic Anhydride.*—Bromine (7·3 g.) in glacial acetic acid (16 c.c.) was added during 3 hr. to a solution of the above anhydride (3 g.) dissolved in acetic acid (7 c.c.) at 115°. This temperature was maintained for a further 19 hr., the solution then evaporated under reduced pressure, and the residue heated at 200—220° until evolution of hydrogen bromide ceased (20 hr.). The residue was boiled with acetic anhydride for 3 hr. After removal of the solvent under reduced pressure, 1·4 g. of yellow solid was sublimed from the residue (bath-temp. 160—200°/0·1 mm.). Recrystallisation from benzene gave 4-*acetoxynaphthalene*-1 : 2-*dicarboxylic anhydride*, m. p. 184—186°, pale-buff needles (Found : C, 64·9; H, 3·0. $C_{14}H_8O_5$ requires C, 65·6; H, 3·15%). Treatment of the anhydride with methanol gave a *half-ester*, m. p. 137—138°, needles from benzene (Found : C, 62·4; H, 4·2. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%). Ultraviolet spectra are tabulated.

Naphthalene-1 : 2-dicarboxylic anhydride				4-Acetoxynaphthalene-1 : 2-dicarboxylic anhydride			
mμ	log ε	mμ	log ε	mμ	log ε	mμ	log ε
256	4·74	344	3·54	258	4·67	345	3·61
308	3·59	354	3·45	309	3·58	355	3·56
322	3·56	360	3·50	324	3·67	362	3·59

9-*Acetoxy*-$\Delta^{1:9(11)}$-*decahydro*-1 : 4-*dioxophenanthrene.*—A solution of benzoquinone (2·2 g.) in dry thiophen-free benzene (20 c.c.) was added to a solution of 1-1′-acetoxyvinyl*cyclo*hexene (5 g.) in the same solvent (20 c.c.) containing a few crystals of quinol. The mixture rapidly

darkened and after 4 days at room temperature a small amount of precipitate was filtered off. After a further 2 days at room temperature the mixture was heated under reflux for 1 hr. and then evaporated under reduced pressure (15 min.). Addition of light petroleum (b. p. 60—80°) to the partially solid residue completed precipitation of the solid which was filtered off and washed with a little ether, to give 9-*acetoxy*-$\Delta^{2:9(14)}$-*decahydro*-1 : 4-*dioxophenanthrene* (3·2 g.), m. p. 110—118°. Recrystallisation from ether gave pale yellow prisms, m. p. 118—120° (rapid heating). On slow heating it melted at 115—120°, resolidified at a higher temperature, and finally melted at 224° (Nazarov [8] records m. p. 120—121°) (Found : C, 69·9; H, 6·7. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%), absorption max. in EtOH at 226, 280, 345 mμ (log ε 4·02, 2·38, 1·90). With acid or alkali it gave dark solutions, and with 2 : 4-dinitrophenylhydrazine (see above) a yellow precipitate which rapidly changed to an amorphous dark red powder.

Degradation of 9-*Acetoxy*-$\Delta^{2:9(14)}$-*decahydro*-1 : 4-*dioxophenanthrene*.—This compound (2·9 g.) was added *via* a Soxhlet extraction apparatus (8 hr. required) to a boiling suspension of lithium aluminium hydride (3 g.) in dry ether (180 c.c.). After cooling, water (30 c.c.) was added followed by ice-cold 10% sulphuric acid (50 c.c.). The aqueous layer was continuously extracted with ether for 24 hr. Evaporation of the dried (K_2CO_3) combined ether extracts left a solid (2·0 g.) containing ketonic material (formed a 2 : 4-dinitrophenylhydrazone). The above procedure was repeated with 1·5 g. of lithium aluminium hydride, and the resulting non-ketonic material dehydrated at 180° for 45 min. in a stream of nitrogen with powdered fused potassium hydrogen sulphate (3 g.). After addition of water the product was extracted with ether and dried (K_2CO_3). The ether was replaced by toluene and the solution heated under reflux with sodium. After cooling and filtering, the solvent was removed, and the residue (1·2 g.) boiled with diphenylamine (6 g.) and 5% palladium–charcoal (1·5 g.) in nitrogen for 16 hr., more catalyst (1·0 g.) being added after 8 hr. The cooled mixture was diluted with ether and filtered, and the diphenylamine precipitated with dry hydrogen chloride. The residue obtained on removal of the ether was chromatographed in light petroleum (b. p. 60—80°) on alumina (Peter Spence type " H "). The eluted phenanthrene (0·6 g.), after two recrystallisations from alcohol and sublimation, had m. p. and mixed m. p. 95—96°. The derived picrate had m. p. and mixed m. p. 143—146°.

9-*Acetoxy*-$\Delta^{2:9(14)}$-*decahydro*-3 : 12-*dimethyl*-1 : 4-*dioxophenanthrene*.—A solution of 1-1′-acetoxyvinyl*cyclo*hexene (16·6 g.), 2 : 6-xyloquinone (12·0 g.), and quinol (0·4 g.) in absolute alcohol (130 c.c.) was heated under reflux for 21 hr., then cooled and filtered. Evaporation under reduced pressure (15 mm.) gave 9-*acetoxy*-$\Delta^{2:9(14)}$-*decahydro*-3 : 12-*dimethyl*-1 : 4-*dioxophenanthrene* (13·1 g.), m. p. 108—111° after washing with light petroleum (b. p. 40—60°) and a little ether. Recrystallisation from light petroleum (b. p. 60—80°) raised the m. p. to 112—113° (Found : C, 71·7; H, 7·4. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%). Ultraviolet absorption maxima (in *cyclo*hexane) were at 240, 274, and 355 mμ (log ε 4·07, 2·07, and 1·79). Extension of the reaction time did not increase the yield. The use of benzene as a solvent reduced the yield.

Degradation of 9-*Acetoxy*-$\Delta^{2:9(14)}$-*decahydro*-3 : 12-*dimethyl*-1 : 4-*dioxophenanthrene*.—This compound (7·8 g.) was reduced and dehydrated as was 9-acetoxy-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene. The product (6·0 g.) (a solid sparingly soluble in ether), however, was filtered off. It (4·6 g.) was dehydrogenated by selenium (13 g.) at 350° for 24 hr. The cold residue was extracted with benzene, filtered, and after replacement of the solvent by xylene, heated under reflux with sodium for 45 min., then cooled and filtered. The residue left on removal of the solvent was split by distillation into several arbitrary fractions, b. p. 100—120°/10^{-3} mm., some of which solidified. The solid had m. p. 56—59°, undepressed on admixture with 3-methylphenanthrene, m. p. 61—62°. The whole distillate on treatment with picric acid in benzene gave 3-methylphenanthrene picrate, m. p. 136—137·5° (from alcohol) raised to 137—138·5° on admixture with an authentic specimen (m. p. 138—139·5°).

4-*Methyl*-1-*phenethyl*cyclo*hexan*-1-*ol*.—4-Methyl*cyclo*hexanone (35·9 g.) was added slowly to an ice-cooled solution of the Grignard reagent from phenethyl bromide (54 g.) and magnesium (9·6 g.) in ether (200 c.c.). The mixture was heated under reflux for 3 min., left overnight for 24 hr., and poured on ice and ammonium chloride. The aqueous layer was extracted with ether. Distillation of the dried ($MgSO_4$) combined extracts gave 4-*methyl*-1-*phenethyl*cyclo*hexan*-1-*ol* (34·1 g.), b. p. 104—110°/0·15 mm., n_D^{20} 1·5200—1·5250. A redistilled sample had b. p. 113°/0·1 mm., n_D^{20} 1·5254 (Found : C, 82·7; H, 10·2. $C_{15}H_{22}O$ requires C, 82·5; H, 10·2%). Bergs *et al.*[21] record b. p. 179°/22 mm. but no analysis.

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-3-*methylphenanthrene*.—The above alcohol (17·1 g.)

[20] Hirshberg and Jones, *Canad. J. Res.*, 1949, **27**, *B*, 437.
[21] Bergs, Wittfield, and Wildt, *Ber.*, 1934, **67**, 238.

was added slowly with stirring to ice-cold 85% sulphuric acid (36 c.c.). After 15 minutes' stirring at room temperature the mixture was extracted with light petroleum (b. p. 60—80°), and the extract washed with cold 85% sulphuric acid, 10% sodium carbonate solution, and 10% sodium sulphate solution, and dried (K_2CO_3). After removal of the solvent the residue was distilled from sodium, to yield 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-3-*methylphenanthrene* (13·0 g.), b. p. 86°/0·1 mm., n_D^{12} 1·5406 (Found: C, 90·6; H, 9·6. $C_{15}H_{20}$ requires C, 89·9; H, 10·0%).

3-*Methylphenanthrene*.—A mixture of the above octahydromethylphenanthrene (7·4 g.) and selenium (17·4 g.) was heated at 320° for 15 hr. On cooling, the mixture solidified and was extracted with benzene. The filtered solution was concentrated and treated with excess of a benzene solution of picric acid. The picrate formed was filtered off and decomposed by adsorption, from benzene solution, on a column of alumina to yield, by elution with light petroleum (b. p. 40—60°), 3-methylphenanthrene (4·5 g.), m. p. 61·5—62·5° (from aqueous alcohol) (picrate, m. p. 138—139·5). Haworth [22] records m. p. 62—63° and a picrate, m. p. 137—138°.

Δ^{3}-*Dodecahydro*-3 : 12-*dimethyl*-1 : 4 : 9-*trioxophenanthrene*.—A solution of 9-acetoxy-$\Delta^{3:9(14)}$-dodecahydro-3 : 12-dimethyl-1 : 4-dioxophenanthrene (1 g.) in methanol (125 c.c.), concentrated sulphuric acid (0·5 c.c.), and water (40 c.c.) was boiled for 4 hr. After removal of the methanol, by distillation, the solution was extracted with ether, and the extract washed with sodium hydrogen carbonate solution, then with saturated sodium chloride solution, and dried (K_2CO_3). Evaporation yielded Δ^{3}-*dodecahydro*-3 : 12-*dimethyl*-1 : 4 : 9-*trioxophenanthrene* (0·6 g.) as a lemon-yellow solid, m. p. 154—159° [from light petroleum (b. p. 60—80°)] (Found: C, 73·7; H, 7·7. $C_{18}H_{20}O_3$ requires C, 73·8; H, 7·7%), absorption max. in *cyclo*hexane at 241, infl. at 270 mμ (log ε 4·08 and 3·16 respectively).

9-*Acetoxy*-$\Delta^{9(14)}$-*dodecahydro*-3 : 12-*dimethyl*-1 : 4-*dioxophenanthrene*.—Zinc powder (1 g.) was added, at room temperature, to a stirred solution of 9-acetoxy-$\Delta^{3:9(14)}$-decahydro-3 : 12-dimethyl-1 : 4-dioxophenanthrene (1 g.) in glacial acetic acid (50 c.c.). After 10 min. the solution was filtered, and the filtrate evaporated under reduced pressure. 9-*Acetoxy*-$\Delta^{9(14)}$-*dodecahydro*-3 : 12-*dimethyl*-1 : 4-*dioxophenanthrene* (0·6 g.), m. p. 131—135°, was extracted from the residue with hot light petroleum (b. p. 100—120°). Crystallisation from methanol raised the m. p. to 136—137° (Found: C, 71·0; H, 8·2. $C_{18}H_{24}O_4$ requires C, 71·0; H, 8·0%).

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[22] Haworth, *J.*, 1932, 1125.

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870. *Thiadiazoles. Part IV.*[1] *The Oxidation of N-(Aroylamidino)thioureas.*

By FREDERICK KURZER.

Oxidative cyclisation of *N*-(aroylamidino)thioureas (I) by hydrogen peroxide in acid yields the expected 5-amino-3-aroylamino-1 : 2 : 4-thiadiazoles (II), but affords 3-amino-5-aryl-1 : 2 : 4-thiadiazoles (III), with simultaneous evolution of carbon dioxide, in the absence of acid. Mixtures of the two products (II, III) result when bromine, or hydrogen peroxide in media of intermediate acidity, is employed.

Some properties, particularly degradations, of 3-amino-5-aryl-1 : 2 : 4-thiadiazoles and their acyl derivatives are described.

PREVIOUS parts of this series [1] have dealt with the synthesis of 1 : 2 : 4-thiadiazoles by oxidative cyclisation of amidinothiourea and its *N*-mono- and *NN'*-di-substituted homologues. This paper describes the normal, as well as the anomalous, behaviour of *N*-(aroylamidino)thioureas (I) in this general reaction.

N-(Aroylamidino)thioureas (I) were prepared, according to the method of Kaiser,

[1] Parts I—III, Kurzer, (*a*) *J.*, 1955, 1; (*b*) *J.*, 1955, 2288; (*c*) *J.*, 1956, 2345.

Thurston, and their co-workers,[2] by the addition of the elements of hydrogen sulphide to *N*-aroyl-*N'*-cyanoguanidines, R·CO·NH·C(:NH)·NH·CN. The sensitivity of these cyanamido-derivatives, particularly to hydrolysis, precluded their isolation in the pure state. When treated without delay with hydrogen sulphide in ethanol, however, the crude intermediates afforded moderate to fair yields of the required thioureas (I). *N*-(Aroylamidino)thioureas were desulphurised by sodium plumbite almost instantly on slight warming.

In the presence of an equivalent of hydrochloric acid, hydrogen peroxide oxidised *N*-(aroylamidino)thioureas (I) to 5-amino-3-aroylamino-1 : 2 : 4-thiadiazoles (II). This formulation is based on the known ease with which compounds incorporating the –C(:NH)·NH·CS– system in their structure, including amidinothioureas,[1] thioaroylguanidines,[3] and *N*-arylimidoarylthioamides,[4] are cyclised to 1 : 2 : 4-thiadiazoles. The structure (II) assigned is in agreement with the ultimate composition, molecular weights, and chemical behaviour of the oxidation products: thus, 5-amino-3-benzamido-1 : 2 : 4-thiadiazole was desulphurised only very slowly by sodium plumbite; it gave benzoic acid on alkaline hydrolysis, and benzaldehyde together with hydrogen sulphide on reduction with zinc and alcoholic hydrochloric acid. The above cyclisation thus provides a route to monoacyl derivatives (II) not otherwise available, since acylation of the parent compound, 3 : 5-diamino-1 : 2 : 4-thiadiazole, yields di- and tri-substituted products directly.[1b]

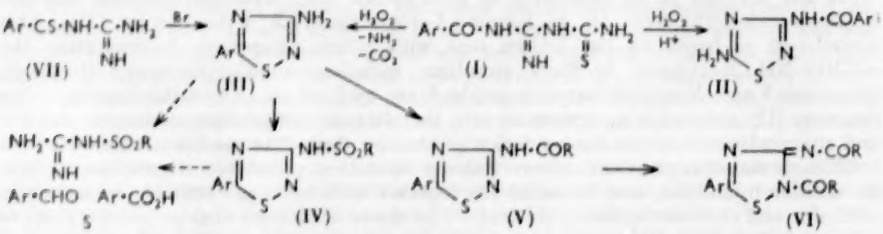
In the absence of mineral acid, however, the oxidation of *N*-(aroylamidino)thioureas took a different and unexpected course, proceeding with simultaneous fission and ring closure to afford excellent yields of 3-amino-5-aryl-1 : 2 : 4-thiadiazoles (III). The parent compound (III; Ar = Ph) of this series, for example, was rapidly formed in 80% yield on treatment of *N*-(benzoylamidino)thiourea in boiling ethanol with an excess of peroxide, carbon dioxide being vigorously evolved, particularly after the addition of the first equivalent of the oxidising agent. The decisive influence of the acidity of the medium in controlling the direction of the cyclisation was clearly shown by the results of a series of oxidations [of (I; Ar = Ph)] employing intermediate concentrations of mineral acid: mixtures of the two possible oxidation products, 5-amino-3-benzamido- (II; Ar = Ph) and 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (III; Ar = Ph), were obtained, the proportion of the former increasing, and that of the latter decreasing, as the quantity of mineral acid present was raised (cf. Table, p. 4530).

It was therefore not unexpected that bromine, another excellent reagent for cyclising amidinothioureas to 1 : 2 : 4-thiadiazoles,[1c] also oxidised *N*-(benzoylamidino)thiourea to the same mixture [of (II and III; Ar = Ph)]. In the initially neutral medium, cyclisation (I) ⟶ (III) should predominate in the opening stages; the simultaneous liberation of hydrogen bromide raises the acidity of the medium, so that the alternative cyclisation (I) ⟶ (II) presently becomes the main reaction: the two products (II, III; Ar = Ph) are in fact obtained in approximately equal yields.

The structure of 3-amino-5-aryl-1,2 : 4-thiadiazoles was assigned on the basis of the properties and degradation of the phenyl homologue and its derivatives (IV, V, VI). The parent compound (III; Ar = Ph) was a base, capable of forming mono- and di-acyl derivatives. Its resistance to alkylation by methyl iodide (absence of thiol [5]), and to desulphurisation by lead plumbite was in accord with a structure incorporating sulphur in a ring system. The product was remarkably stable towards hydrolysis: it was cleaved only very slowly by boiling concentrated sodium hydroxide or hydrochloric acid, sulphur (or hydrogen sulphide) and benzoic acid being the main products isolated. Reduction by zinc and hydrochloric acid gave benzaldehyde and hydrogen sulphide. These observations established the linking of the aryl radical to a carbon atom. The presence of the guanidino-grouping, suggested by the occasional isolation of minute quantities of guanidine in hydrolysis experiments, was clearly shown by the reduction of the toluene-*p*-sulphonyl derivative (IV; R = *p*-C_6H_4Me) to toluene-*p*-sulphonylguanidine in good yield. All this evidence, together with the ultimate composition and molecular weight of the product,

[2] Adams, Kaiser, Nagy, Peter, Sperry, and Thurston, *J. Org. Chem.*, 1952, **17**, 1162.
[3] Goerdeler and Fincke, *Chem. Ber.*, 1956, **89**, 1033.
[4] Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1928, **7**, 237.
[5] Fromm, *Annalen*, 1893, **275**, 20; Fairfull and Peak, *J.*, 1955, 803.

and its non-identity with the known 5-amino-3-phenyl-1 : 2 : 4-thiadiazole,[6] indicated the high probability of its having the isomeric 3-amino-5-aryl structure (III; Ar = Ph). Meanwhile, decisive proof for this view became available by Goerdeler and Fincke's [3] very recent unequivocal synthesis, from thiobenzoylguanidine (VII), of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole, with which the phenyl homologue of the present series of compounds (III) proved to be identical.



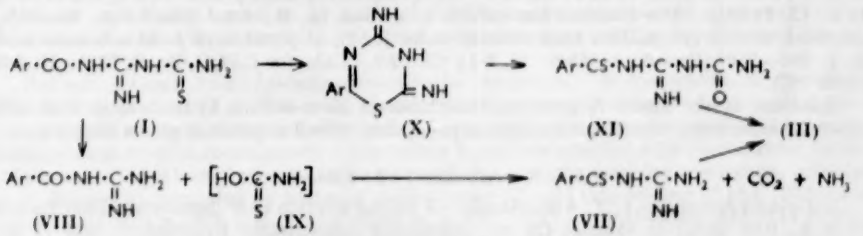
In view of the considerable reactivity [1b,3] of the 3-amino-group in the 1 : 2 : 4-thiadiazole system, monoacyl compounds are formulated as 3-acylamino-derivatives (IV, V). A tautomeric displacement of hydrogen into the 4-position being inadmissible, the easily accessible dibenzoyl derivative is represented as 3-benzimido-2-benzoyl-2 : 3-dihydro-5-phenyl-1 : 2 : 4-thiadiazole (VI; R = Ph). Attention is drawn to the result of the reduction of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (III) and its 3-toluene-*p*-sulphonyl derivative (IV), neither of which is cleaved solely at the $S_{(1)}$–$N_{(2)}$ bond, as are 3 : 5-diamino-derivatives; [1] in this respect, the *C*-arylated 1 : 2 : 4-thiadiazoles approach the behaviour of " Hector's bases." [7]

The smooth cyclisation (I) ⟶ (III) is remarkable for its rapidity and for the absence of side reactions, in spite of its being necessarily a multistage process. Whatever the mechanism of this reaction, the immediate precursor of the final product (III) is almost certain to incorporate the thioaroylguanidino-grouping, from which the 1 : 2 : 4-thiadiazole ring system may arise by dehydrogenation in the usual way. Of the possible routes that would account for the initial stages, attention may be drawn to a preliminary hydrolytic removal from the starting material (I) of the elements of (hypothetical) thiocarbamic acid (IX) which may (either directly, or in the form of nascent carbon oxysulphide) change the remaining benzoylguanidine (VIII) into the required precursor (VII). The well-known conversion of benzoyl into thiobenzoyl derivatives by means of phosphorus pentasulphide [8] or aluminium sulphide,[9] and the established mobility of the sulphur atoms in thion-[10] and dithio-carboxylic [11] acids and their derivatives would appear to lend support to this view. A mechanism involving the initial removal, from the reactant (I), of the terminal thioamide group by its complete oxidation to sulphur is ruled out, since benzoylguanidine (VIII) failed to yield 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (III) on treatment, under the usual experimental conditions, with hydrogen peroxide in the presence of sulphur (the latter being provided in the form of either hydrogen sulphide or an ethanolic solution of the element).

An interesting alternative possibility involves the cyclic dehydration of the starting material to the substituted 1 : 3 : 5-thiadiazine (X), which, followed by hydration across the $S_{(1)}$–$C_{(2)}$ bond, would furnish the thiobenzoylguanidino-compound (XI) directly. It is well established that the nucleus of related 1 : 3 : 5-thiadiazines is cleaved relatively easily.[12]

[6] Goerdeler, *Chem. Ber.*, 1954, **87**, 57, 66.
[7] Hector, *Ber.*, 1892, **25**, ref. 799.
[8] Kindler, *Annalen*, 1923, **431**, 209; Gatewood and Johnson, *J. Amer. Chem. Soc.*, 1926, **48**, 2904; Miyamichi, *J. pharm. Soc. Japan*, 1928, **48**, 114.
[9] Kindler and Finndorf, *Ber.*, 1921, **54**, 1079.
[10] Jepson, Lawson, and Lawton, *J.*, 1955, 1791.
[11] Todd, Bergel, and Karimullah, *J.*, 1936, 1557; Kjaer, *Acta Chem. Scand.*, 1950, **4**, 1347; 1952, **6**, 27, 1374.
[12] Wagner-Jauregg, *Annalen*, 1948, **561**, 87.

However, the absence, amongst the reaction products, of at least small proportions of 5-phenyl-3-ureido-1 : 2 : 4-thiadiazole [presumably the primary oxidation product of (XI)] casts doubt on this interpretation, because the necessary further degradation of the substituted urea to the amine (III) is unlikely to be rapid and complete. Experiments on the mechanism of this cyclisation (I) ⟶ (III) are being continued.



The benzoylguanidine required in this work was readily prepared in consistent, if moderate, yields by the interaction of guanidine hydrochloride and benzoyl chloride at 190—220°. This adaptation of Korndörfer's method [13] avoids the use of pressure equipment which had previously been regarded [13] as essential.

Experimental

Picrates were prepared from equimolar proportions of the appropriate amidinothioureas or 1 : 2 : 4-thiadiazoles and picric acid in hot or boiling ethanol. Light petroleum was of boiling range 60—80°.

N-(*Aroylamidino*)*thioureas*.

N-(Benzoylamidino)thiourea was prepared from dicyandiamide by the method of Adams *et al.*[3] in 46—54% (overall) yield and formed, after two crystallisations from ethanol, deep yellow lustrous cubes, m. p. 170—171° (decomp.) (Found: C, 48·6; H, 4·8; N, 25·2. Calc. for $C_9H_{10}ON_4S$: C, 48·65; H, 4·5; N, 25·2%). Its *picrate* formed deep-yellow prisms, m. p. 206—207° (decomp.) (from ethanol) (Found: C, 40·1; H, 2·9. $C_{15}H_{13}O_9N_7S$ requires C, 39·9; H, 2·9%).

N-(p-*Nitrobenzoylamidino*)*thiourea*.—Dicyandiamide (12·6 g., 0·15 mole) was dissolved in a solution of potassium hydroxide (85%; 20 g., 0·3 mole) in water (50 ml.) and diluted with acetone (50 ml.). The stirred liquid was treated, during 20 min., with a solution of *p*-nitrobenzoyl chloride (25 g., 0·135 mole) in acetone (60 ml.) kept at <10°. The resulting suspension was diluted with water (to a total volume of 2 l.) and acidified with concentrated hydrochloric acid (25 ml.). The finely divided precipitate was collected on a large Buchner funnel and successively washed with water and a little ethanol (filtration slow). The thoroughly drained crude intermediate *N*-*p*-nitrobenzoyl-*N'*-cyanoguanidine was suspended in absolute ethanol (250 ml.), and treated with hydrogen sulphide during 5 hr. at 50—60°. The finely divided white reactant gradually changed to an orange-yellow crystalline light material and a deep scarlet heavy crystalline deposit. The latter (m. p. 201—202°; 4·35—5·45 g., 12—15%) was readily isolated by decantation of the supernatant suspension; two crystallisations from acetone–ethanol gave scarlet prisms of N-(p-*nitrobenzoylamidino*)*thiourea*, m. p. 203—204° (decomp.) (Found: C, 39·9; H, 3·8; N, 26·5; S, 11·5. $C_9H_9O_3N_5S$ requires C, 40·45; H, 3·4; N, 26·2; S, 12·0%). The orange-yellow by-product, and the material remaining in the ethanol solution, were non-homogeneous. The *picrate* formed dark orange needles, m. p. 197—198° (decomp.) (from aqueous ethanol) (Found: C, 36·35; H, 2·6. $C_{15}H_{12}O_{10}N_6S$ requires C, 36·3; H, 2·4%).

N-(p-*Chlorobenzoylamidino*)*thiourea*.—Dicyandiamide (0·075 mole) and *p*-chlorobenzoyl chloride (11·8 g., 0·0675 mole) were condensed under the conditions detailed immediately above, and the intermediate crude *N*-*p*-chlorobenzoyl-*N'*-cyanoguanidine was suspended in ethanol (150 ml.), treated with hydrogen sulphide [1 hr. each at 25°, 40°, 50°, and 65°]. The resulting orange suspension was filtered at the pump while hot (solid: A), the filtrate evaporated nearly to dryness in a vacuum, and the residue dissolved in boiling acetone (40—60 ml.). The colourless plates which separated on addition of an equal volume of light petroleum, and cooling, were removed and rinsed with a little light petroleum (solid: B). By repeating this process, further

[13] Korndörfer, *Archiv Pharm.*, 1903, **241**, 476.

fractions of colourless platelets were removed, if necessary. The more soluble product, crystallising slowly from the concentrated acetone solution on addition of light petroleum and partial evaporation, consisted of successive fractions (total 6—7·8 g., 35—45%) of orange granular material, which gave, after crystallisation from ethanol–light petroleum, orange-yellow prisms of N-(p-*chlorobenzoylamidino*)*thiourea*, m. p. 152—154° (decomp.) (Found: C, 42·1; H, 3·55; N, 21·6; S, 11·9; Cl, 13·6. $C_9H_9ON_4SCl$ requires C, 42·1; H, 3·5; N, 21·8; S, 12·5; Cl, 13·8%). The fractions less soluble in acetone (A, B; total 2·5—3·5 g., 24—33%) consisted, after crystallisation from ethanol–water (2 : 1), of platelets of *p*-chlorobenzoic acid, m. p. 236—238° (Found: C, 53·6; H, 3·1; Cl, 22·7. Calc. for $C_7H_5O_2Cl$: C, 53·7; H, 3·2; Cl, 22·7%).

Solutions of the above *N*-(aroylamidino)thioureas in N-sodium hydroxide, treated with aqueous lead acetate, rapidly gave a copious precipitate of lead sulphide on gentle warming.

5-Amino-3-aroylamino-1 : 2 : 4-thiadiazoles.

5-Amino-3-benzamido-1 : 2 : 4-thiadiazole.—A boiling solution of *N*-(benzoylamidino)thiourea (2·22 g., 0·01 mole) in ethanol (20 ml.) containing concentrated hydrochloric acid (1 ml., 0·01 mole) was treated with 6% hydrogen peroxide (17 ml., 0·03 mole) during 5 min. (colour change from deep to pale yellow). Most of the ethanol was removed by distillation under reduced pressure during 5 min. and separation of the crystalline product completed by storage at 0°. Two crystallisations from acetone–ethanol afforded scales of *5-amino-3-benzamido-1 : 2 : 4-thiadiazole*, m. p. 215—217° (sintering at 208°) (yield, including material from the mother-liquors, 1·32 g., 60%) [Found: C, 49·3; H, 3·4; N, 25·5; S, 14·7%; *M* (cryoscopically, in thymol), 210. $C_9H_8ON_4S$ requires C, 49·1; H, 3·6; N, 25·45; S, 14·5%; *M*, 220].

A solution of the product in N-sodium hydroxide, treated with aqueous lead acetate, remained clear after 3 minutes' boiling. In boiling 3N-alkali, finely divided lead sulphide was slowly deposited. Reduction of 5-amino-3-benzamido-1 : 2 : 4-thiadiazole (conditions as for III, R = Ph; see below) gave benzaldehyde (isolated as the 2 : 4-dinitrophenylhydrazone) in 56% yield.

5-Amino-3-p-nitrobenzamido-1 : 2 : 4-thiadiazole.—Addition of hydrogen peroxide (3 × 0·005 moles) to *N*-(*p*-nitrobenzoylamidino)thiourea (1·34 g., 0·005 mole) in boiling ethanol (60 ml.)–hydrochloric acid (0·5 ml., 0·005 mole), followed by addition of the mixture to water (250 ml.), gave a flocculent yellow precipitate. This was coagulated by warming, collected (dry wt., 1·05 g.), and crystallised from ethanol–benzene–acetone (2 : 2 : 1; 500 ml.). The separated yellow microcrystalline powder (0·64 g., 48%) was *5-amino-3-p-nitrobenzamido-1 : 2 : 4-thiadiazole*, m. p. 258—260° (decomp.) (Found: C, 40·45; H, 2·75; N, 26·2; S, 11·8. $C_9H_7O_3N_6S$ requires C, 40·75; H, 2·6; N, 26·4; S, 12·1%). Partial evaporation of the filtrates gave a little more of the above product, and finally deposited (0·17 g., 15%) the more soluble 3-amino-5-*p*-nitrophenyl-1 : 2 : 4-thiadiazole, m. p. 233—235° (see below), formed as by-product.

5-Amino-3-p-chlorobenzamido-1 : 2 : 4-thiadiazole.—" Acidic " oxidation of *N*-(*p*-chlorobenzoylamidino)thiourea (1·28 g., 0·005 mole) (as described for the *p*-nitro-derivative) gave a white granular powder. After being extracted with boiling ethanol (25 ml.), the undissolved material was twice crystallised from boiling nitrobenzene–ethanol and gave white platelets of *5-amino-3-p-chlorobenzamido-1 : 2 : 4-thiadiazole*, m. p. 260—262° (decomp.) (Found: C, 42·35; H, 2·6; N, 21·7; S, 12·7; Cl, 13·6. $C_9H_7ON_4SCl$ requires C, 42·4; H, 2·75; N, 22·0; S, 12·6; Cl, 13·9%).

3-Amino-5-aryl-1 : 2 : 4-thiadiazoles.

3-Amino-5-phenyl-1 : 2 : 4-thiadiazole.—A boiling solution of *N*-(benzoylamidino)thiourea (6·65 g., 0·03 mole) in ethanol (50 ml.) was treated with 6% hydrogen peroxide (51 ml., 0·09 mole) in three portions at 3 min. intervals. After the addition of the second equivalent, the original deep yellow colour of the solution was completely discharged; carbon dioxide was evolved throughout the oxidation. The colourless liquid was evaporated to half its bulk in a vacuum, and the white crystals were collected after storage at 0° during 12 hr. Two crystallisations from ethanol (8 ml. per g.) or water (250 ml. per g.) gave lustrous elongated prisms (or needles, respectively) of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole, m. p. and mixed m. p. (with material prepared by the method of Goerdeler and Fincke [3]) 132—134° (yield, including material from the mother-liquors, 4·0—4·35 g., 75—82%) [Found: C, 53·8, 53·7; H, 3·8, 4·0; N, 23·5, 24·0, 23·9; S, 17·7%; *M* (cryoscopically in naphthalene) 195, (in thymol) 180. Calc. for $C_8H_7N_3S$: C, 54·2; H, 4·0; N 23·7; S, 18·1%; *M*, 177). In a blank experiment no carbon dioxide was evolved in the absence of *N*-(benzoylamidino)thiourea by the otherwise identical reaction mixture.

The *picrate*, prepared in either boiling ethanol or warm 3N-hydrochloric acid, by the use of either one or two equivs. of picric acid, crystallised from ethanol as yellow blades, m. p. 148—150° (Found: C, 41·4; H, 3·2; N, 20·8; S, 7·0. $C_{14}H_{10}O_7N_6S$ requires C, 41·4; H, 2·5; N, 20·7; S, 7·9%).

3-Acetamido-5-phenyl-1 : 2 : 4-thiadiazole, prepared from the amino-compound, formed platelets, m. p. 147—149° (Found: C, 54·8; H, 4·2. Calc. for $C_{10}H_9ON_3S$: C, 54·8; H, 4·1%). Goerdeler and Fincke [3] give m. p. 143°. 3-*p*-Aminobenzenesulphonamido-5-phenyl-1 : 2 : 4-thiadiazole consisted of needles, m. p. 193—194° (after sintering at 187°); Goerdeler and Fincke [3] give m. p. 187°.

3-*Amino-5-phenyl*-1 : 2 : 4-*thiadiazole.*—*Alkaline hydrolysis.* A suspension of the finely powdered reactant (1·77 g., 0·01 mole) in 20% w/w aqueous potassium hydroxide (45 g.) was refluxed until all the material had dissolved (2·5 hr.), and boiling was continued for 1 hr. more; ammonia was evolved continuously. The yellow liquid was acidified with concentrated hydrochloric acid (15 ml.) (evolution of hydrogen sulphide), and the resulting precipitate, collected at 0° (filtrate A), separated by means of boiling water (25 ml.) into sulphur (0·18 g., 56%) and benzoic acid (0·80 g., 65%), m. p. and mixed m. p. 119—121°. More benzoic acid (0·11 g., 9%) was recovered from filtrate A by extraction with ether.

In ethanolic 15% potassium hydroxide, almost half the reactant was recovered after 3 hours' refluxing.

Acid hydrolysis. A solution of the reactant (0·01 mole) in hydrochloric acid (constant-boiling mixture; 40 ml.) was refluxed during 5 hr. Hydrogen sulphide was slowly evolved, while the resulting turbidity gradually gave place to yellow globules. The boiling clear aqueous phase was readily decanted from the sulphur (0·24 g., 75%); the solid separating from the solution (0°) was benzoic acid, m. p. and mixed m. p. 119—121° (from water) (0·85 g., 70%). The filtrate therefrom was treated with toluene-*p*-sulphonic acid monohydrate (1 g.); the non-homogeneous solid (0·45 g.) which appeared on partial spontaneous evaporation was fractionated from ethanol and gave (in some but not all experiments) guanidine toluene-*p*-sulphonate, m. p. and mixed m. p. 225—226° (0·18 g., 8%). The final aqueous filtrate contained much ammonium salt.

More than half of the reactant was recovered unchanged when its solution in 3N-hydrochloric acid was refluxed during 1 hr.

Reduction. A solution of the reactant (0·01 mole) in boiling ethanol (40 ml.) containing zinc foil (4 g.) was treated during 5 min. with concentrated hydrochloric acid (4 ml.), and refluxed for another 10 min. (evolution of hydrogen sulphide). The decanted ethanolic solution was concentrated in a vacuum (smell of benzaldehyde) and treated with 2 : 4-dinitrophenylhydrazine (2 g., 0·01 mole), dissolved in ethanol (30 ml.) containing concentrated hydrochloric acid (5 ml.). The orange granular precipitate (m. p. 231—234; 1·86 g., 65%) was benzaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 235—236° (from acetone–ethanol).

3-Amino-5-phenyl-1 : 2 : 4-thiadiazole (0·005 mole) was recovered unchanged after being refluxed with methyl iodide (0·15 mole) in methanol during 2 hr. The product very gradually deposited traces of lead sulphide on prolonged boiling in 3N-sodium hydroxide containing lead acetate.

3-*Benzamido-5-phenyl*-1 : 2 : 4-*thiadiazole.*—Addition of benzoyl chloride (0·7 g., 0·005 mole) to a solution of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (0·88 g., 0·005 mole) in pyridine (15 ml.), and storage of the liquid at 100° during 30 min., followed by its addition to N-hydrochloric acid (150 ml.) at 0°, gave a white granular solid. Crystallisation from ethanol gave lustrous needles of 3-*benzamido-5-phenyl*-1 : 2 : 4-*thiadiazole*, m. p. 154—155° (0·85 g., 61%) (Found: C, 64·1; H, 3·7; N, 14·6; S, 11·0. $C_{15}H_{11}ON_3S$ requires C, 64·1; H, 3·9; N, 14·95; S, 11·4%).

With an excess of benzoyl chloride (4·22 g., 0·03 mole) the reactant (0·005 mole) gave, under identical conditions and treatment, a viscous oil. The supernatant aqueous phase was discarded, the oil heated with ethanol (15 ml.), and the white granular solid, which separated instantly, collected at 0° (m. p. 205—210°; 1·75 g., 90%). Two crystallisations from benzene–ethanol (50 : 15 ml.) gave prisms of 3-*benzimido-2-benzoyl*-2 : 3-*dihydro-5-phenyl*-1 : 2 : 4-*thiadiazole*, m. p. 215—217° (Found: C, 68·9; H, 4·2; N, 10·4; S, 7·6. $C_{22}H_{15}O_2N_3S$ requires C, 68·6; H, 3·9; N, 10·9; S, 8·3%).

3-p-*Nitrobenzamido-5-phenyl*-1 : 2 : 4-*thiadiazole*, similarly prepared from equivalent quantities of the reactants in pyridine, crystallised from acetone–ethanol as pale yellow platelets, m. p. 210—212° (75%) (Found: C, 55·0; H, 3·4; N, 17·1; S, 9·7. $C_{15}H_{10}O_3N_4S$ requires C, 55·2; H, 3·1; N, 17·2; S, 9·8%).

5-*Phenyl*-3-*toluene*-p-*sulphonamido*-1 : 2 : 4-*thiadiazole.*—A solution of the amino-compound

(3·54 g., 0·02 mole) in pyridine (50 ml.), treated with toluene-*p*-sulphonyl chloride (11·4 g., 0·06 mole), was kept at 100° during 0·5 hr. The solid obtained when the mixture was poured into 2N-hydrochloric acid (300 ml.) at 0° was twice crystallised from acetone–benzene–ethanol (1 : 1 : 1; carbon) and yielded platelets of *5-phenyl-3-toluene*-p-*sulphonamido*-**1 : 2 : 4**-*thiadiazole*, m. p. 206—208° (4·3—4·75 g., 65—72%) (Found: C, 54·0, 54·3; H, 4·2, 3·9; N, 12·7; S, 19·0. $C_{15}H_{13}O_2N_3S_2$ requires C, 54·4; H, 3·9; N, 12·7; S, 19·3%). The use of a larger excess of sulphonyl chloride (6 mols.) gave again only the monosulphonyl derivative, in somewhat improved (75—80%) yields.

Reduction. A boiling suspension of the derivative (1·66 g., 0·005 mole) in ethanol (40 ml.) containing zinc turnings (4 g.) was treated with concentrated hydrochloric acid (6 × 1 ml., at 3 min. intervals) and refluxing continued for a total of 45 min. The reactant rapidly dissolved, and hydrogen sulphide was evolved. The decanted, filtered liquid was concentrated (to 10 ml.) in a vacuum and diluted with 3N-hydrochloric acid (10 ml.), and the clear (absence of starting material) liquid made alkaline with 3N-sodium hydroxide. The collected thick precipitate was washed with a little water, then dried, and the product separated from the zinc oxide by exhaustive extraction with boiling ethanol (6 × 10 ml.). The combined filtered extracts gave, on concentration, crystals (m. p. 202—204°; 0·69 g., 60%) which afforded, by one crystallisation from ethanol, needles of toluene-*p*-sulphonylguanidine hydrate, m. p. and mixed m. p. 204—205° (Found: C, 41·6; H, 5·4. Calc. for $C_8H_{11}O_2N_3S,H_2O$: C, 41·6; H, 5·6%).

Oxidation of N-(*Benzoylamidino*)*thiourea by Bromine.*—A solution of the reactant (2·22 g., 0·01 mole) in ethanol (30 ml.) at 40—45° was treated with bromine (1·6 g., 0·01 mole) in chloroform (5 ml.). The decolorised liquid was distilled to half its bulk in a vacuum, the residual solution stirred into water (120 ml.), and the collected dried product (1·95 g.) dissolved in 1 : 1 ethanol–acetone (120 ml.). The separated crystals were 5-amino-3-benzamido-**1 : 2 : 4**-thiadiazole (0·9 g., 41%), forming platelets, m. p. and mixed m. p. (with material prepared by " acidic " hydrogen peroxide oxidation) 215—217°, on further crystallisation (Found: C, 49·2; H, 3·5%). The filtrates therefrom, distilled to small bulk (10 ml.), deposited 3-amino-5-phenyl-**1 : 2 : 4**-thiadiazole (0·62 g., 35%), m. p. and mixed m. p. (with material prepared by " neutral " hydrogen peroxide oxidation) 132—133° (from ethanol).

Oxidation of N-(*Benzoylamidino*)*thiourea by Hydrogen Peroxide in Media of Differing Acidities.*—Oxidation of the reactant (0·01 mole) in ethanol containing different amounts of hydrochloric acid, followed by separation of the products as described immediately above, gave the following results:

Equivs. of acid	0·05	0·10	0·50	0·66	0·80
Yield (%) of (II; Ar = Ph)	3	5	35	45	50
Yield (%) of (III; Ar = Ph)	80	70	27	9	—

3-*Amino*-5-p-*nitrophenyl*-**1 : 2 : 4**-*thiadiazole*.—To *N*-(*p*-nitrobenzoylamidino)thiourea (1·33 g., 0·005 mole) in boiling ethanol (40 ml.) containing 1 drop of 3N-hydrochloric acid, 6% hydrogen peroxide (8·5 ml., 0·015 mole) was added during 6 min. The deep scarlet liquid became light orange, while carbon dioxide was evolved. The yellow solid which separated towards the end of the reaction was collected at 0° (m. p. 224—228°; 1·0 g., 90%) and gave, on two crystallisations from acetone–ethanol (60 and 20 ml. respectively, followed by evaporation on the steam bath until crystallisation just set in), yellow needles of 3-*amino*-5-p-*nitrophenyl*-**1 : 2 : 4**-*thiadiazole*, m. p. 234—236° [Found: C, 42·9, 43·4; H, 2·8, 2·8; N, 25·0; S, 14·6%; *M* (cryoscopically in thymol), 210. $C_8H_6O_2N_4S$ requires C, 43·2; H, 2·7; N, 25·2; S, 14·4%; *M*, 222]. Attempts to obtain the picrate were unsuccessful, the unchanged thiadiazole being recovered when its ethanolic or acetone solution was treated with picric acid (1 equiv.) in ethanol.

3-*Amino*-5-p-*chlorophenyl*-**1 : 2 : 4**-*thiadiazole*.—" Neutral " oxidation of *N*-(*p*-chlorobenzoylamidino)thiourea (1·28 g., 0·005 mole) (as described for the *p*-nitro-derivative) gave a white granular solid. This was refluxed with acetone (30 ml.), the suspension quickly filtered at the pump while hot (residue A), and the filtrate evaporated to 10 ml. and diluted with ethanol (10 ml.). Further crystallisation of the separated product from the same solvents gave massive needles (0·60 g., 56%) of 3-*amino*-5-p-*chlorophenyl*-**1 : 2 : 4**-*thiadiazole*, m. p. 196—197° (Found: C, 45·6; H, 2·9; N, 20·0; S, 14·7; Cl, 16·4. $C_8H_6N_3SCl$ requires C, 45·4; H, 2·8; N, 19·9; S, 15·1; Cl, 16·8%). Residue A (0·25 g., 20%) consisted of 5-amino-3-*p*-chlorobenzamido-**1 : 2 : 4**-thiadiazole, m. p. and mixed m. p. (with material prepared by " acidic " oxidation) 260—262° (decomp.) (after crystallisation from nitrobenzene–ethanol).

Benzoylguanidine.—A mixture of guanidine hydrochloride (28·65 g., 0·3 mole) and benzoyl

chloride (42·0 g., 0·3 mole) was kept, during successive 25-min. periods, at 180—185°, 190—195°, and 210—220°. At 190—195° the solid gradually dissolved, reaction being complete when distinct evolution of hydrogen chloride ceased. The yellow viscid liquid was carefully, yet rapidly diluted with ethanol (120 ml.); the resulting yellow solution was quickly filled with crystalline solid which was collected after 6 hr. at room temperature. Crystallisation from ethanol gave white prisms of benzoylguanidine hydrochloride, m. p. 210—212° (after sintering at 206°) (yield, including good material from mother-liquors, 18—21 g., 30—35%). Further crystallisation from water (10 ml. per g., with addition of 2 drops of 3N-hydrochloric acid) gave prisms of the solvated product, m. p. 208—212° (after sintering at 206°) (Found: C, 44·4; H, 5·3. Calc. for $C_8H_9ON_3,HCl,H_2O$: C, 44·15; H, 5·5%).

A solution of the hydrochloride (10·0 g., 0·05 mole) in water (75 ml.), acidified with concentrated hydrochloric acid (0·5 ml.) at 70°, was allowed to cool until crystallisation was about to set in (60°), treated with aqueous 3N-sodium hydroxide (25 ml., 0·075 mole), and quickly cooled. The product, collected at 0°, and pressed between filter-paper, was dissolved in warm acetone (20 ml.), and the filtered solution diluted with light petroleum (30 ml.). The separated benzoylguanidine formed prisms, m. p. 162—164° (yield, including satisfactory material from mother-liquors, 6·1—7·0 g., 75—85%) (Found: C, 59·0; H, 5·9; N, 26·2. Calc. for $C_8H_9ON_3$: C, 58·9; H, 5·5; N, 25·8%).

Interaction of guanidine thiocyanate and benzoyl chloride (1 : 1·1 mol.) in pyridine at 60° or 100° during 30 min. gave mainly intractable oils. Traube's synthesis [14] gave, in our hands, mainly guanidine benzoate, m. p. and mixed m. p. with authentic material [15] 226—228° (after sintering at 220°) (Found: C, 52·6; H, 5·7; N, 22·8. Calc. for $CH_5N_3,C_7H_6O_2$: C, 53·0; H, 6·1; N, 23·2%).

Benzoylguanidine failed to yield 3-amino-5-phenyl-1 : 2 : 4-thiadiazole when the base or its hydrochloride (0·01 mole) in boiling ethanol [either containing dissolved sulphur (0·01 mole) or being simultaneously treated with a slow stream of hydrogen sulphide] was oxidised with hydrogen peroxide (0·03 mole) in the usual manner.

The author thanks the Council of the Chemical Society for a grant from the Research Fund. Grateful acknowledgment is again made to Mr. W. Tertiuk for valuable technical help.

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[*Received, June 11th*, 1956.]

[14] Traube, *Ber.*, 1910, **43**, 3589.
[15] Walker, *J.*, 1949, 1996.

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871. *Amino-sugars and Related Compounds. Part I. The Deamination of* D-*Glucosamine Hydrochloride.*

By B. C. BERA, A. B. FOSTER, and M. STACEY.

Deamination of D-glucosamine hydrochloride with sodium nitrite and hydrochloric acid yields mainly chitose. Reduction of chitose affords crystalline 2 : 5-anhydro-D-mannitol the structure of which is proved, thus confirming the structure of chitose as 2 : 5-anhydro-D-mannose.

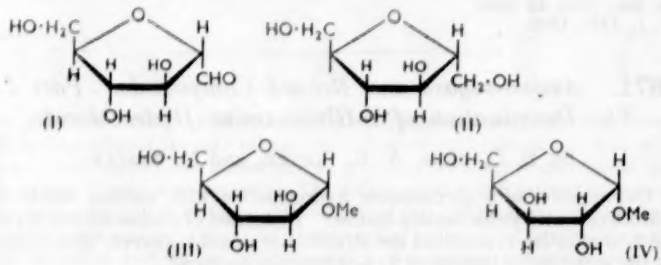
CHITOSE (2 : 5-anhydro-D-mannose) (I), the amorphous product obtained by the action of nitrous acid on D-glucosamine hydrochloride (2-amino-2-deoxy-D-glucose hydrochloride) has long been known.[1] The presence of the 2 : 5-anhydro-ring was inferred [2] when 5-acetoxymethylfuran-2-carboxylic acid was obtained on treatment of chitonic acid (2 : 5-anhydro-D-mannonic acid) with acetic anhydride and sodium acetate. The stereochemical relationship of chitose and chitonic acid has been substantiated recently.[3] Allocation of the D-mannose configuration to chitose followed from the demonstration,[4] by indirect methods, that "isosaccharic acid" (obtained from chitose or chitonic acid by oxidation with nitric acid) was 2 : 5-anhydro-D-mannosaccharic acid. We report herein evidence which substantiates the structure of chitose as 2 : 5-anhydro-D-mannose.

[1] Ledderhose, *Z. physiol. Chem.*, 1880, **4**, 139.
[2] Fischer and Andreae, *Ber.*, 1903, **36**, 2587.
[3] Grant, *New Zealand J. Sci. Technol.*, 1956, **37**, 509.
[4] Levene and La Forge, *J. Biol. Chem.*, 1915, **21**, 345, 351; Levene, *ibid.*, 1918, **36**, 89.

In connection with the deaminative degradation of ψ-heparin [5] it became essential to ascertain the precise course of the deamination reaction and as model compounds D-glucosamine hydrochloride and methyl α- and β-D-glucosaminide (methyl 2-amino-2-deoxy-α- and -β-D-glucopyranoside) have been studied. The results obtained with D-glucosamine hydrochloride are described herein.

D-Glucosamine hydrochloride was deaminated in the presence of sodium nitrite and hydrochloric acid. The course of the reaction could be followed conveniently by zone electrophoresis (ionophoresis *) on paper using an alkaline borate buffer.[6] Chitose was observed to be the main product of reaction along with traces of unidentified substances. D-Glucose, D-mannose, and D-arabinose, which have characteristic ionophoretic behaviour, appeared not to be formed (cf. Grant [3]). Deamination of *trans*-2-amino*cyclo*hexanol, in which the amino-group is predominantly equatorial, yields *cyclo*pentylmethanol in high yield.[7] There is a close analogy between this reaction and the deamination of D-glucosamine hydrochloride; thus, since chitose is the predominant product of the deamination of D-glucosamine hydrochloride, the amino-sugar must be present in the reaction solution as, or must react principally in, the pyranose form, the preferred conformation of which would have the amino-group in an equatorial position. The mechanism of deamination of D-glucosamine hydrochloride suggested by Peat [8] would therefore appear to be the most probable and would be expected to lead to inversion at $C_{(2)}$. The presence of a small amount of the furanose and acyclic forms in equilibrium with the pyranose form of D-glucosamine hydrochloride in solution might account for some or all of the trace products since on deamination they would be expected to give products other than chitose.

In aqueous solutions containing sodium carbonate, sodium hydrogen carbonate, pyridine, ammonia, or methyldi-*n*-octylamine, chitose was converted into a complex mixture containing a main component and traces of nine others. This behaviour, which is being investigated further, emphasises that alkaline conditions must be avoided in the preparation of chitose. It is unlikely that chitose is affected under the conditions of ionophoresis since it has been noted [9] that disaccharides (*e.g.*, nigerose) which are very sensitive to alkali are not decomposed during ionophoresis in a borate buffer at pH 10 although they undergo decomposition in this buffer when not adsorbed on paper.



Chitose is amorphous and relatively few crystalline derivatives are known; [3,8] however, reduction of chitose with sodium borohydride or preferably with hydrogen and Raney nickel gave a good yield of crystalline 2 : 5-anhydro-D-mannitol (II) : ionophoresis revealed the presence of other products also and it is possible that they may have originated by alkaline decomposition of chitose during reduction. Alkaline conditions develop in aqueous

* Subsequent references to ionophoresis imply the use of paper as the electrolyte support and a borate buffer (pH 10) as the electrolyte unless otherwise stated.

[5] Foster, Martlew, and Stacey, *Chem. and Ind.*, 1953, 825; Foster and Huggard, *Adv. Carbohydrate Chem.*, 1955, **10**, 335.
[6] Foster, Newton-Hearn, and Stacey, *J.*, 1956, **30**, and references cited therein.
[7] McCasland, *J. Amer. Chem. Soc.*, 1951, **73**, 2293; cf. Curtin and Schmukler, *ibid.*, 1955, **77**, 1105.
[8] Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37.
[9] Barker, Bourne, and O'Mant, unpublished data cited by Barker, Bourne, and Theander, *J.*, 1955, 4276.

solutions of sodium borohydride and it is of interest that the Raney nickel, prepared by the well known procedure,[10] gave an alkaline reaction when stirred with phenolphthalein although the aqueous washings from the same catalyst were neutral.

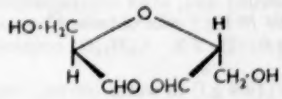
Ionophoresis of the furanoside derivatives shown in the Table indicates that vicinal *cis*- but not vicinal *trans*-hydroxyl and -hydroxymethyl groups in five-membered rings react strongly with borate ions. The low M_G value (0·04) of 2 : 5-anhydro-D-mannitol is consistent with the formula (II) which contains only *trans*-related vicinal hydroxyl and

*M_G values of some furan derivatives.**

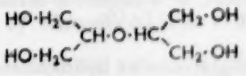
Derivative	M_G value	Derivative	M_G value
Methyl α-D- and α-L-arabofuranoside (III)	0·035	Methyl α-D-xylofuranoside (IV)	0·56
Methyl β-D- and α-L-arabofuranoside	0·035	Methyl β-D-xylofuranoside	0·33
		2 : 5-Anhydro-D-mannitol (II)	0·04

* Ionophoresis was carried out with the apparatus and technique described by Foster (*Chem. and Ind.*, 1952, 1050), on Whatman No. 3 paper in sodium borate (cf. ref. 6) (pH 10) for 2 hr. at a potential gradient of 22 v/cm. Detection was by alkaline silver solution (Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444).

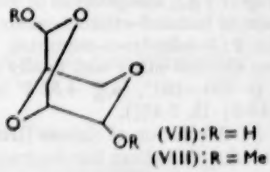
hydroxymethyl groups. Further data supporting the structure (II) for 2 : 5-anhydro-D-mannitol followed from periodate oxidation. The anhydro-derivative (II) rapidly consumed one mol. of periodate without the formation of formic acid or formaldehyde. The rapid uptake is, however, surprising, since the related compound 1 : 4-anhydro-D-threitol, which exhibits the expected behaviour of a vicinal *trans*-glycol, is only slowly oxidised by periodate.[11] The dialdehyde (V) thus obtained from 2 : 5-anhydro-D-mannitol was amorphous but migrated as a single zone in ionophoresis and was optically active. The



(V)



(VI)



(VII): R = H
(VIII): R = Me

latter property substantiates the mannose configuration at $C_{(2)}$ since oxidation of 2 : 5-anhydro-1 : 6-dibenzoyl-D-glucitol with lead tetra-acetate [12] gave an optically inactive dialdehyde. Aqueous solutions of the dialdehyde (V) showed no ultraviolet carbonyl absorption and gave no carbonyl wave on polarography, thus resembling the dialdehyde obtained [13] on periodate oxidation of methyl α-D-glucopyranoside. The latter dialdehyde, however, has one carbonyl group masked by intramolecular hemiacetal formation and the second hydrated. The dialdehyde (V) gave unsatisfactory analyses but from models it appears possible for both carbonyl groups to be involved in intramolecular hemiacetal formation to give a bicyclic system (VII). Each carbonyl-oxygen atom in (V) is separated from a hydroxyl-oxygen atom by 5 atoms and it is known that 5-hydroxypentanal exists predominantly in the hemiacetal form.[14] With methanolic hydrogen chloride the dialdehyde (V) gave a product which, on the basis of methoxyl content and non-reducing character, probably has structure (VIII). The formation of a methyl glycosidic but not a dimethyl acetal type of product in this reaction is strong evidence for the dihemiacetal structure (VII).

Reduction of the dialdehyde (V) with sodium borohydride gave the optically inactive ether (VI), isolated as tetra-acetate. This is also obtained, together with two isomeric

[10] Adkins and Pavlic, *J. Amer. Chem. Soc.*, 1947, **69**, 3039.
[11] Klosterman and Smith, *ibid.*, 1952, **74**, 5336.
[12] Hockett, Zief, and Goepp., *ibid.*, 1946, **68**, 935.
[13] Hurd, Baker, Holysz, and Saunders, *J. Org. Chem.*, 1953, **18**, 186.
[14] Hurd and Saunders, *J. Amer. Chem. Soc.*, 1952, **74**, 5324.

products, by condensation of two molecules of glycerol. Three such products are known [15] but their structures are undetermined.

It is clear that the reactions of 2 : 5-anhydro-D-mannitol described above can only be accommodated by the structure (II). Since it is most unlikely that any stereochemical change occurs in the reduction of chitose to 2 : 5-anhydro-D-mannitol the structure of chitose is substantiated.

Experimental

Deamination of D-Glucosamine Hydrochloride.—The following optimum conditions were established. A solution of D-glucosamine hydrochloride (10·8 g.) in concentrated hydrochloric acid (22·5 ml.) and water (977·5 ml.) was set aside at room temperature for 4—6 hr. (to reach mutarotational equilibrium), then treated with sodium nitrite (27·6 g.) in water (1 l.) at room temperature, and the deamination was followed polarimetrically. Optical rotation was constant after 30 min. and ionophoresis at this point with the apparatus and technique previously described [16] with an acetate buffer (pH 5·0) revealed the absence of D-glucosamine (ninhydrin).

The solution was aerated for 2 hr. under reduced pressure and then passed down a column (60 × 3·3 cm.) of cation-exchanger (Amberlite IR-120, H^+ form; 500 g.). The eluate (3·2 l.) was immediately freed from acid by shaking it several times with a 5% solution of methyldi-*n*-octylamine [17] in chloroform. Excess of amine was removed by further extractions with chloroform and finally with ether. The aqueous solution was concentrated to 250 ml. at <35° (bath)/12—15 mm. and used directly in the reductions. Ionophoresis in borate buffer (pH 10) of the solution after each stage in the purification revealed no change in the content of reducing sugars. In separate experiments chitose was isolated as a viscous syrup.

Reduction of 2 : 5-Anhydro-D-mannose (Chitose).—(*a*) The solution of chitose described above was reduced by hydrogen (40 atm.) in the presence of W-2 Raney nickel catalyst [18] (25 ml. of suspension). The temperature was raised to 95—100° during 4—5 hr. and the solution then left to cool overnight and filtered through carbon. The filtrate, when evaporated, gave a colourless syrup (7·7 g.), ionophoresis of which, and also paper chromatography [irrigation with the organic phase of butanol–ethanol–water–ammonia (40 : 10 : 49 : 1)], revealed traces of substances other than 2 : 5-anhydro-D-mannitol. The syrup crystallized when seeded and, after crystallisation from ethanol–ether and finally ethanol, 2 : 5-*anhydro*-D-*mannitol* (6·1 g.) was obtained having m. p. 100—101°, $[\alpha]_D^{20}$ +58·2° (*c*, 1·37 in H_2O) (Found: C, 44·0; H, 7·2. $C_6H_{12}O_5$ requires C, 43·9; H, 7·4%).

(*b*) A solution of chitose [from D-glucosamine hydrochloride (1·08 g.)] in water (60 ml.) was treated with sodium borohydride (0·24 g.). The solution gave a strongly alkaline reaction and, when a negative Benedict reaction was obtained, excess of sodium borohydride was decomposed with carbon dioxide and the solution evaporated to dryness at 40° (bath)/12—15 mm. The residue was extracted with ethanol (2 × 20—25 ml.), and the combined extracts were evaporated to a pale yellow syrup. Ionophoresis of this product revealed appreciable amounts of substances other than 2 : 5-anhydro-D-mannitol which latter could be isolated from the syrup in low yield as described in (*a*).

Behaviour of Chitose in Alkaline Media.—Sodium carbonate, sodium hydrogen carbonate, pyridine, and ammonia were severally added to solutions of chitose prepared as described above. Ionophoresis of the solutions after 24 hr. at room temperature showed some disappearance of chitose (M_G value 0·07) and the appearance of an unidentified product (M_G value 0·62). In preliminary attempts to isolate chitose, pyridine extracts of the sugar were concentrated during 30 min. at 40° (bath)/12—15 mm. Ionophoresis of the residue revealed a complex mixture. The main components were chitose and the product of M_G value 0·62; there were nine other products (M_G values: 0·33, 0·55, 0·70, 0·79, 0·82, 0·91, 0·99, 1·06, 1·12). Attempted fractionation on charcoal–celite and cellulose columns was unsuccessful.

Periodate Oxidation of 2 : 5-Anhydro-D-mannitol.—The consumption of oxidant at room temperature in aqueous 0·075M-sodium metaperiodate (50 ml.) containing 2 : 5-anhydro-D-mannitol (0·101 g.) was found by standard procedures (cf. Klosterman and Smith [11]) to be essentially complete after 15 min. (1·02 mols. of oxidant consumed). Neither formic acid nor formaldehyde was produced.

[15] Levene and Walti, *J. Biol. Chem.*, 1927, **75**, 325; 1928, **77**, 685; Lewis, *J. Soc. Chem. Ind.*, 1922, **41**, 99T; cf. Rayner, *ibid.*, 1922, **41**, 224T.

[16] Foster, *Chem. and Ind.*, 1952, 1050.

[17] Lester Smith and Page, *J. Soc. Chem. Ind.*, 1948, **67**, 48; cf. Hughes and Williamson, *Biochem. J.*, 1951, **48**, 487.

The dialdehyde (V) ($[\alpha]_D$ *ca.* +30° in water), isolated by evaporation and extraction of the residue with alcohol, strongly reduced Benedict's solution, decomposed on attempted distillation, gave a single, reducing component on ionophoresis,[18] showed no absorption in the range 230—350 mμ, and gave no carbonyl reduction wave on polarography.[18]

A solution of the crude dialdehyde (V), obtained after periodate oxidation of **2 : 5**-anhydro-D-mannitol (2·4 g.) in 2% w/v methanolic hydrogen chloride (100 ml.), was boiled under reflux for 6 hr. then neutralised with silver carbonate and worked up in the usual way. Distillation of the residue gave **2 : 6-*dimethoxy*-3 : 7 : 9-*trioxo*bicyclo[3 : 3 : 1]*nonane*** (VIII) (0·61 g.), b. p. 120—125° (bath)/0·02 mm., n^{20} 1·4538, $[\alpha]_D^{20}$ +62·72° (*c.* 1·12 in MeOH) (Found : MeO, 31·9, 32·3, 32·6. $C_9H_{12}O_5$ requires MeO, 32·6%). Acidic hydrolysis regenerated the dialdehyde (V).

Reduction of the Dialdehyde (V).—A solution of the dialdehyde [obtained from **2 : 5**-anhydro-D-mannitol (1·0 g.) by essentially method (*b*)] in water (50 ml.) was treated with sodium borohydride (0·25 g.) at room temperature. The solution rapidly lost its optical activity and reducing power towards Benedict's solution. After 30 min. the excess of borohydride was decomposed by carbon dioxide, the solution evaporated to dryness, and the dried (*in vacuo* over P_2O_5) residue acetylated in pyridine (10 ml.) with acetic anhydride (4 ml.). Isolation in the usual way gave a syrupy product from which *di*-(2-*hydroxy*-1-*hydroxymethylethyl*) *ether* (VI) was obtained as a colourless, viscous liquid (0·7 g.), b. p. 190—200° (bath)/0·01—0·05 mm., n^{23} 1·4425 (Found : Ac, 51·2. $C_{14}H_{22}O_9$ requires Ac, 51·5%). The tetra-acetate was optically inactive.

We thank Professor E. Berner for samples of the methyl xylo- and arabo-furanoside. The expenses of this investigation were covered by a grant from the Nuffield Foundation. One of us (B. C. B.) thanks the Government of India for a grant.

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EDGBASTON, BIRMINGHAM, 15. [*Received, June 27th*, 1956.]

[18] Linstead, Elvidge, and Whalley, "A Course in Modern Techniques of Organic Chemistry," Butterworths, London, 1955, p. 161.

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872. *Synthetical Experiments in the Chelidonine–Sanguinarine Group of the Alkaloids. Part IV.*[1]

By A. S. BAILEY and C. R. WORTHING.

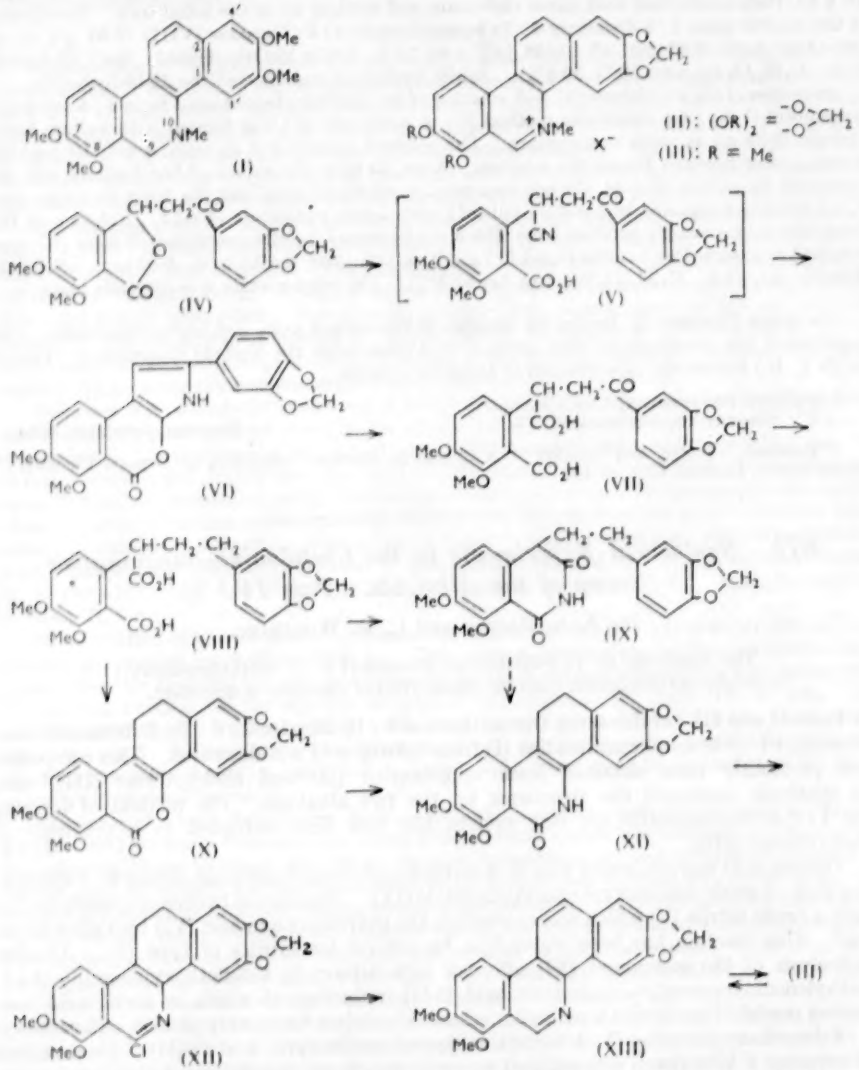
The synthesis of **7 : 8**-dimethoxy-**10**-methyl-**2′ : 3′**-methylenedioxy-**1 : 2**-benzophenanthridinium chloride (chelerythrine chloride) is described.

IN Parts II and III [1] of this series the synthesis of **9 : 10**-dihydro-**7 : 8 : 2′ : 3′**-tetramethoxy-**10**-methyl-**1 : 2**-benzophenanthridine (I) from opianic acid was described. This compound had previously been obtained from sanguinarine (II) and chelerythrine (III),[2] and its synthesis confirmed the structures for the two alkaloids. The method of forming the **1 : 2**-benzophenanthridine ring system has now been extended to a synthesis of chelerythrine (III).

Opianic acid was condensed with **3 : 4**-methylenedioxyacetophenone, giving **6 : 7**-dimethoxy-**3**-(**3 : 4**-methylenedioxyphenacyl)phthalide (IV). Addition of hydrogen cyanide to this gave a crude nitrile (V) which was cyclised to the pyrrolo*iso*coumarin (VI) by hydrochloric acid. This reaction has been shown [3] to be general for nitriles of type (V). Alkaline hydrolysis of the compound (VI) afforded α-(2-carboxy-**3 : 4**-dimethoxyphenyl)-γ-(**3 : 4**-methylenedioxyphenyl)-γ-oxobutyric acid (VII), reduction of which in acetic acid containing perchloric acid with a palladium–charcoal catalyst [4] smoothly yielded α-(2-carboxy-**3 : 4**-dimethoxyphenyl)-γ-(**3 : 4**-methylenedioxyphenyl)butyric acid (VIII). This method of reducing a keto-group was selected to avoid the drastic conditions of the Clemmensen

[1] Part II, Bailey and Robinson, *J.*, 1950, 1375; Part III, Bailey, Robinson, and Staunton, *ibid.*, p. 2277.
[2] Späth and Kuffner, *Ber.*, 1931, **64**, 2034.
[3] Bailey and Staunton, *J.*, 1952, 2153; Bailey and Swallow, *J.*, 1956, 2477.
[4] Rosenmund and Karg, *Ber.*, 1942, **75**, 1850; Kindler, Metzendorf, and Dschi-yin-Kwok, *Ber.*, 1943, **76**, 308; Baker and Jenkins, *J. Amer. Chem. Soc.*, 1946, **68**, 2102; Johnson and Graber, *ibid.*, 1950, **72**, 925.

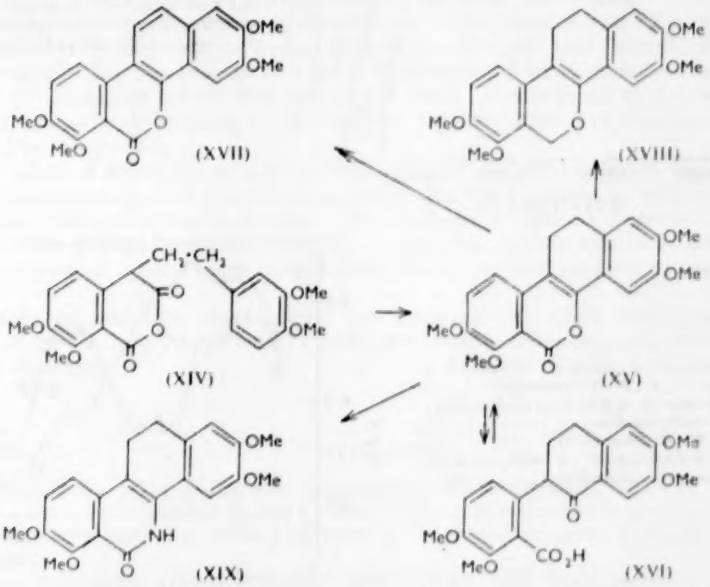
or Wolff–Kishner method. Heating the ammonium salt of the acid (VIII) gave the homophthalimide (IX). Unfortunately, treatment of this with polyphosphoric acid failed to give the desired product (XI): the dark amorphous material obtained gave an intense colour with ferric chloride, indicating loss of the methylenedioxy-group. The cyclisation could also not be accomplished by using boron trifluoride or hydrogen fluoride.



Preliminary experiments were then carried out with α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-dimethoxyphenyl)butyric acid and its anhydride (XIV) since they were available [1] from previous work. Heating either with polyphosphoric acid afforded the dihydronaphtho*iso*coumarin (XV), a reaction analogous to the formation of 3-phenyl*iso*coumarin from homophthalic anhydride and benzene in the presence of aluminium chloride.[5]

[5] Graebe and Trümpy, *Ber.*, 1898, **31**, 375.

The infrared spectrum of the product (XV) contained a band at 1721 cm.$^{-1}$, expected of an enol ester; and the compound was rapidly hydrolysed to the keto-acid (XVI), which re-formed the *iso*coumarin above its melting point. The structure (XV) was supported by dehydrogenation to the fully aromatic compound (XVII). The latter was also obtained from the keto-acid (XVI) on treatment with thionyl chloride followed by ammonia in an attempt to make its amide; this reaction must involve chlorination followed by removal of hydrogen chloride. Reduction of the *iso*coumarin (XV) with lithium aluminium hydride at room temperature yielded the naphtho*iso*chromen (XVIII) which did not contain a keto- or hydroxy-group (infrared spectrum): reduction of homophthalic anhydride with lithium aluminium hydride [6] gives some *iso*chroman as well as the expected glycol, and Conover and Tarbell [7] have observed that reduction, by lithium aluminium hydride, of aromatic ketones having methoxy- or amino-groups *para* to the carbonyl group reduces the latter to methylene. The formation of the *iso*chromen (XVIII) from the *iso*coumarin (XV) is similar to the formation of a dialkylchromen on reaction of a Grignard reagent with an *iso*coumarin.[8]



Heating the dihydronaphtho*iso*coumarin (XV) at 150° with a solution of ammonia [9] in ethanol gave a satisfactory yield of the dihydro-1 : 2-benzophenanthridone (XIX), identical with the compound obtained in Part II of this series.[1]

Having established this method of obtaining the 1 : 2-benzophenanthridine ring system we applied it to the acid (VIII). Heating the latter with polyphosphoric acid gave amorphous dark material, and so the acid was converted into its chloride, which was then cyclised with stannic chloride at 0°, giving the dihydronaphtho*iso*coumarin (X). The infrared spectrum of this contained a band at 1733 cm.$^{-1}$ (enol lactone), and its ultraviolet spectrum was almost identical (see diagram) with that of the analogue (XV). Alkaline hydrolysis gave the corresponding keto-acid which could not be obtained free from solvent of crystallisation, but when heated above its melting point gave the *iso*coumarin (X). The

[6] Anderson and Holliman, *J.*, 1950, 1037.
[7] Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3586; cf. "Organic Reactions," Vol. VIII, Wiley, New York, 1953, pp. 269, 283.
[8] Ghosh, Todd, and Wilkinson, *J.*, 1940, 1393.
[9] Gabriel, *Ber.*, 1885, **18**, 2433, 3470; 1886, **19**, 830, 1653.

latter was recovered unchanged after being heated at 150° with ethanolic ammonia, although these conditions sufficed for the transformation of the analogue (XV) into the phenanthridone (XIX); this is probably due to the fact that the *iso*coumarin (X) is much higher-melting and less soluble in organic solvents than its analogue. However, in ethylene glycol containing ammonia the benzophenanthridone (XI) was produced at 210°, and refluxing the phenanthridone with phosphorus oxychloride yielded the 9-chloro-derivative (XII). When hydrogen was bubbled through a boiling *p*-cymene solution of this

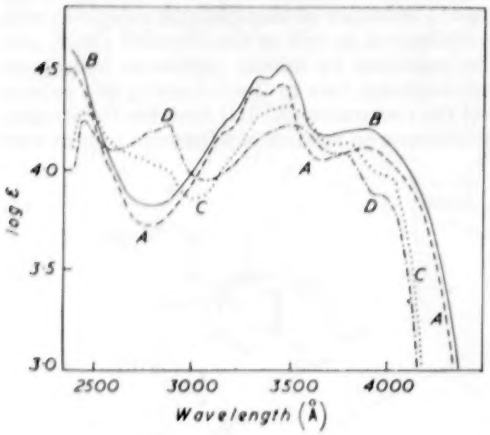


FIG. 1. *Absorption spectra of*: 3′:4′-*dihydro*-7:8:6′:7′-*tetramethoxy*-(— — —)(*A*) *and* 3′:4′-*dihydro*-7:8-*dimethoxy*-6′:7′-*methylenedioxynaphtho*(1′:2′-3:4)*iso*-*coumarin* (——) (*B*); 3:4-*dihydro*-7:8:2′:3′-*tetramethoxy*- (. . . .) (*C*) *and* 3:4-*dihydro*-7:8-*dimethoxy*-2′:3′-*methylenedioxy*-1:2-*benzophenanthridone* (— . — . —) (*D*) (*all in* $CHCl_3$).

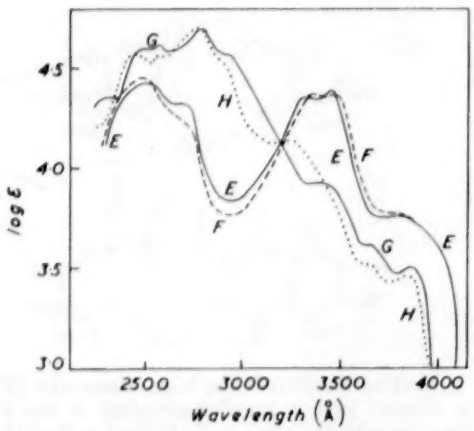


FIG. 2. *Absorption spectra of*: 9-*chloro*-3:4-*dihydro*-7:8:2′:3′-*tetramethoxy* (——) (*E*), 9-*chloro*-3:4-*dihydro*-7:8-*dimethoxy*-2′:3′-*methylenedioxy*- (— — —) (*F*), 7:8:2′:3′-*tetramethoxy*- (——) (*G*), *and* 7:8-*dimethoxy*-2′:3′-*methylenedioxy*-1:2-*benzophenanthridine* (. . . .) (*H*).

containing palladium–charcoal, the chlorine atom was removed and the compound simultaneously dehydrogenated. This method had previously [1] been used on the tetramethoxy-analogue of (XII). The product, 7:8-dimethoxy-2′:3′-methylenedioxy-1:2-benzophenanthridine (XIII), was identical (m. p., mixed m. p., infrared spectrum, R_F value) with the material obtained by sublimation of chelerythrine chloride at 200°/0·05 mm.; the decomposition of a quaternary ammonium chloride to give an alkyl chloride is a well-known reaction.[10] Sarkar [11] has observed that sanguinarine chloride loses methyl chloride

[10] "Sidgwick's Organic Chemistry of Nitrogen," Taylor and Baker, Oxford Univ. Press, 1937, pp. 28, 553; for recent examples in alkaloid chemistry see: Karrer and Schmid, *Helv. Chim. Acta*, 1946, **29**, 1853; Gellért, Raymond-Hamet, and Schlittler, *ibid.*, 1951, **34**, 642; Schlittler and Hohl, *ibid.*, 1952, **35**, 29; Ewing, Hughes, Ritchie, and Taylor, *Nature*, 1952, **169**, 618.

[11] S. N. Sarkar, D.Phil. Thesis, Oxford, 1948, p. 61.

at 240°, giving the corresponding tertiary base. The base (XIII) with dimethyl sulphate in xylene gave the methosulphate which was not purified but was dissolved in water and on addition of hydrochloric acid then yielded chelerythrine chloride (III; X = Cl), identical (mixed m. p. and R_F value) with the natural product. The compound gave analyses as for the trihydrate, but after drying for 2 hr. at 100° for the monohydrate. Analyses have been reported for the anhydrous salt,[12, 13] the monohydrate,[12, 14] trihydrate,[15] tetrahydrate,[16] and pentahydrate.[16, 17] The ψ-cyanide was also prepared, identical (mixed m. p. and infrared spectrum) with a specimen obtained from the natural product. The infrared spectra of chelerythrine ψ-cyanide and sanguinarine ψ-cyanide do not contain a band at 2400—2100 cm.$^{-1}$. An example of the compound which contains a ·CN group and does not show any absorption in this region has been reported.[18]

It is interesting that the melting points of the compounds (X), (XI), and (XII) are higher than those of their tetramethoxy-analogues; but (XIII) is lower-melting than its tetramethoxy-analogue. The spectra of (X), (XI), (XII), and (XIII) are shown in the Figures, along with those of the corresponding tetramethoxy-compounds.

The separation of chelerythrine and sanguinarine, and the chemical detection of small quantities of one compound as a contaminant of the other, are difficult. We have found that the two alkaloids can easily be separated by paper chromatography using butanol–acetic acid–water, sanguinarine having R_F 0·64 (orange spot) and chelerythrine R_F 0·72 (yellow spot). The two substances could not be separated when phenol–water was used since both substances moved with the solvent front. It was found that a specimen of chelerythrine chloride supplied by Dr. Manske contained a trace of sanguinarine, easily detected by this method.

The colour of chelerythrine salts has been variously described as lemon-yellow, golden-yellow, orange-yellow, and orange. This may be due to contamination with sanguinarine or to the different hydrates formed. The synthetic compound sometimes appeared lemon-yellow, at other times orange-yellow. A drop of an aqueous solution of chelerythrine chloride placed on a filter paper gave a clear yellow spot with no trace of orange in the colour.

Added, September 27th, 1956.—Slavík and Slavíková (*Coll. Czech. Chem. Comm.*, 1954, **20**, 21) separated chelerythrine from sanguinarine by paper chromatography with butanol–acetic acid–water.

Experimental

Ultraviolet absorption spectra were determined in chloroform unless otherwise stated, and infrared spectra were measured on Nujol mulls. Paper chromatograms were run on Whatman No. 1 paper with butan-1-ol–acetic acid–water (4 : 1 : 5), and examined in visible and ultraviolet light.

1-(3 : 4-Methylenedioxyphenyl)ethanol[19] was oxidised with finely powdered potassium permanganate[20] in acetone solution to 3 : 4-methylenedioxyacetophenone, b. p. 170—190°/18 mm., m. p. 86—87° (from methanol).

6 : 7-*Dimethoxy*-3-(3 : 4-*methylenedioxyphenacyl*)*phthalide* (IV).—3 : 4-Methylenedioxyacetophenone (35 g.) was dissolved in warm ethanol (250 c.c.) containing opianic acid (42 g.), and potassium hydroxide (21 g.) in water (35 c.c.) was added dropwise. The orange-coloured solution was kept at room temperature for 36 hr., then acidified with dilute hydrochloric acid. The oil which separated rapidly solidified; it was collected, washed with water, and crystallised

[12] Karrer, *Ber.*, 1917, **50**, 212.
[13] Govindachari and Thyagarajan, *J.*, 1956, 769.
[14] Bauer and Hedinger, *Arch. Pharm.*, 1920, **258**, 167.
[15] Gadamer and Stichel, *ibid.*, 1924, **262**, 494.
[16] König and Tietz, *ibid.*, 1893, **231**, 145, 161.
[17] Cannon, Hughes, Ritchie, and Taylor, *Austral. J. Chem.*, 1953, **6**, 86.
[18] Potts and Robinson, *J.*, 1955, 2466.
[19] Böttcher, *Ber.*, 1909, **42**, 253; Balfe, Downer, Evans, Kenyon, Poplett, Searle, and Tárnoky, *J.*, 1946, 801.
[20] Richardson, Robinson, and Seijo, *J.*, 1937, 835.

from acetic acid–methanol, forming white felted needles (59 g.), m. p. 152—153° (Found: C, 64·0; H, 4·5. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%).

During one preparation the material separated as a yellow solid, obviously the αβ-unsaturated ketone; attempted crystallisation from ethanol gave the colourless cyclisation product (IV).

7 : 8-*Dimethoxy*-5′-(3 : 4-*methylenedioxyphenyl*)*pyrrolo*(2′ : 3′-3 : 4)*isocoumarin* (VI).—6 : 7-Dimethoxy-3-(3 : 4-methylenedioxyphenacyl)phthalide (20 g.) was dissolved in boiling 2-methoxyethanol (70 c.c.) containing crystalline sodium acetate (8 g.). To the mixture, at 100°, potassium cyanide (10 g.) in water (20 c.c.) was added during 2 min. through a funnel reaching to the bottom of the flask. After 10 minutes' heating with occasional stirring, the mixture was cooled and dilute hydrochloric acid (200 c.c.) added. Thirty minutes later the aqueous liquor was decanted from the gum which had separated; the gum was then washed with distilled water by decantation and dissolved in boiling acetic acid (70 c.c.), and 17% hydrochloric acid (20 c.c.) added. A yellow precipitate immediately separated. The mixture was then heated on a water-bath for 5 min. and, after cooling, the solid *product* was collected, washed with dilute acetic acid, then with methanol, and dried (9—13 g.; m. p. 280—286°). Two crystallisations from pyridine gave yellow needles, m. p. 287—289° (decomp.) (Found: C, 65·7; H, 3·9; N, 3·9. $C_{20}H_{15}O_6N$ requires C, 65·8; H, 4·1; N, 3·8%), $\lambda_{max.}$ 2370 (ε 24,800), 3240 (ε 20,500), and 4100 Å (ε 8080).

α-(2-*Carboxy*-3 : 4-*dimethoxyphenyl*)-γ-(3 : 4-*methylenedioxyphenyl*)-γ-*oxobutyric Acid* (VII).—7 : 8-Dimethoxy-5′-(3 : 4-methylenedioxyphenyl)pyrrolo(2′ : 3′-3 : 4)*iso*coumarin (20 g.) was refluxed with 10% sodium hydroxide solution (200 c.c.). An orange-red solution was formed as the lactone dissolved, ammonia was evolved, and the solution became pale yellow. When the evolution of ammonia ceased (2—3 hr.), the solution was filtered and acidified with dilute hydrochloric acid. The gum which separated slowly solidified. Crystallisation from 50% acetic acid gave the *acid* as colourless rods (15·2 g.), m. p. 181—183° (decomp.) (Found: C, 59·9; H, 4·6. $C_{20}H_{18}O_9$ requires C, 59·7; H, 4·5%). The *anhydride* formed clusters of rods (from acetic acid), m. p. 194—195° (Found: C, 62·8; H, 4·0. $C_{20}H_{16}O_8$ requires C, 62·5; H, 4·2%).

α-(2-*Carboxy*-3 : 4-*dimethoxyphenyl*)-γ-(3 : 4-*methylenedioxyphenyl*)*butyric Acid* (VIII).—A solution of the foregoing acid (5 g.) in acetic acid (40 c.c.) containing 60% perchloric acid (0·5 c.c.) was hydrogenated at 60°/1 atm. in the presence of 5% palladium–charcoal (1 g.); two mols. of hydrogen were absorbed during 1·5 hr. The catalyst was filtered off, water (20 c.c.) added, the solution evaporated *in vacuo* to *ca.* 10 c.c., and then more water (10 c.c.) added. An oil separated which slowly solidified (3·4 g.; m. p. 148—150°). Crystallisation from toluene or 50% ethanol gave the *acid* as colourless rhombs, m. p. 150—152° (decomp.) (Found: C, 61·8; H, 5·1%; equiv., 194. $C_{20}H_{20}O_8$ requires C, 61·9; H, 5·2%; equiv., 194).

Reduction of α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-dimethoxyphenyl)-γ-oxobutyric acid by the same method gave α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-dimethoxyphenyl)-butyric acid, m. p. 169—171°, not depressed by a specimen obtained [1] by Clemmensen reduction.

7 : 8-*Dimethoxy*-4-(3 : 4-*methylenedioxyphenylethyl*)*homophthalimide* (IX).—The acid (VIII) (2 g.) was dissolved in ammonia (3 c.c.; *d* 0·88), and the solution evaporated to dryness *in vacuo*. Ammonium carbonate (0·5 g.) was added and the mixture heated for 30 min. *in vacuo* at 160° (oil-bath). The temperature of the bath was then raised to 190° for 15 min. and the resulting glass crystallised from benzene. The *imide* formed rods, m. p. 131—132° (Found: C, 65·1; H, 5·2; N, 3·8. $C_{20}H_{19}O_6N$ requires C, 65·1; H, 5·2; N, 3·8%), and gave a yellow colour with sodium hydroxide solution.

3′ : 4′-*Dihydro*-7 : 8-*dimethoxy*-6′ : 7′-*methylenedioxynaphtho*(1′ : 2′-3 : 4)*isocoumarin* (X).—A mixture of α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-methylenedioxyphenyl)butyric acid (6 g.) and chloroform (75 c.c.) was heated under reflux and thionyl chloride (40 c.c.) slowly added. After 10 min. the yellow solution was evaporated on a water-bath *in vacuo*, the residual gum dissolved in hot chloroform (30 c.c.), and stannic chloride (7 c.c.) added to the ice-cold solution. A dark gum immediately separated which crystallised at 0°. After 4 hr. the supernatant liquid was decanted and the solid triturated with 17% hydrochloric acid and chloroform. The organic layer was separated, the aqueous layer was extracted with chloroform, and the combined extracts were washed with dilute hydrochloric acid, dilute sodium hydroxide solution (which removed some dark-coloured impurity), and water. Removal of the solvent gave a pale brown solid (3·9 g.). 3′ : 4′-*Dihydro*-7 : 8-*dimethoxy*-6′ : 7′-*methylenedioxynaphtho*-(1′ : 2′-3 : 4)*isocoumarin* separated from acetic acid as yellow needles which softened at 230—233°, m. p. 240—243°. This behaviour on heating still occurred after the compound had been crystallised from anisole, 2-methoxyethanol, or pyridine, and after chromatography on alumina

(Found : C, 68·5; H, 4·6. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%), $\lambda_{max.}$ 3340 (ε 27,950), 3475 (ε 32,000), and 3850 Å (ε 15,700). The infrared spectrum had bands at 1733, 1645, and 1605 cm.$^{-1}$.

2-(2-*Carboxy*-3 : 4-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy*-1-*oxonaphthalene*.—3′ : 4′-Dihydro-7 : 8-dimethoxy-6′ : 7′-methylenedioxynaphtho(1′ : 2′-3 : 4)*iso*coumarin (X) (0·5 g.) was refluxed with 2N-sodium hydroxide solution (25 c.c.) and ethanol (10 c.c.). The material slowly dissolved, and after 1 hr. the clear solution was diluted with water (75 c.c.), filtered, and acidified with dilute hydrochloric acid. The solid tetralone which separated was crystallised twice from ethyl acetate, forming colourless plates of *solvate* which, dried at 100°/0·05 mm., had m. p. 154—155° (decomp.) [Found : C, 63·8, 64·1; H, 5·4, 5·6. $(C_{20}H_{18}O_7)_2,C_4H_8O_2$ requires C, 63·8; H, 5·4%]. Crystallisation of the acid from toluene gave another *solvate*, as colourless prisms, m. p. 175—178° (decomp.) [Found : C, 68·2; H, 5·3. $(C_{20}H_{18}O_7)_2,C_7H_8$ requires C, 67·8; H, 5·3%]. The acid rapidly formed the *iso*coumarin (X) at its m. p.

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridone* (XI).—3′ : 4′-Dihydro-7 : 8-dimethoxy-6′ : 7′-methylenedioxynaphtho(1′ : 2′-3 : 4)*iso*coumarin (0·5 g.) and ethylene glycol (15 c.c.) containing anhydrous ammonia (3 g.) were heated together for 17 hr. at 210° (sealed tube). The mixture was diluted with ethanol, and the solid collected, washed with ethanol, and crystallised from pyridine (0·38 g.; m. p. 290—292°). Crystallisation from anisole gave 3 : 4-*dihydro*-7 : 8-*dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridone* in the form of pale yellow plates, m. p. 292—295° (decomp.) (Found : C, 68·7; H, 5·1; N, 3·6. $C_{20}H_{17}O_5N$ requires C, 68·4; H, 4·9; N, 4·0%), $\lambda_{max.}$ 2450 (ε 17,600), 2880 (ε 16,760), 3520 (ε 16,200), 3790 (ε 11,900), and 3990 Å (ε 7260); infrared bands were at 3077 (broad band), 1639, and 1625 cm.$^{-1}$.

9-*Chloro*-3 : 4-*dihydro*-7 : 8-*dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridine* (XII).—The preceding phenanthridone (1 g.) and phosphorus oxychloride (25 c.c.) were refluxed (oil-bath) together for 1 hr., the orange solution cooled and poured on ice, and excess of dilute ammonia solution added. The resulting solid was collected, washed with water, and dried. The material was extracted with boiling toluene, the extracts were evaporated, and the residue was crystallised from ethyl acetate, giving the *chloro-compound* (0·62 g.), pale yellow needles, m. p. 226—228° (Found : C, 65·3; H, 4·5; N, 3·8; Cl, 9·3. $C_{20}H_{16}O_4NCl$ requires C, 65·0; H, 4·4; N, 3·8; Cl, 9·6%), $\lambda_{max.}$ 2475 (ε 28,450), 3340 (ε 22,850), 3450 (ε 24,480), and 3760 Å (ε 5980).

7 : 8-*Dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridine* (XIII).—(*a*) Chelerythrine chloride was sublimed at 200°/0·05 mm. The pale yellow sublimate was crystallised from toluene and then from 1 : 1 butan-1-ol–2-methoxyethanol, forming colourless plates, m. p. 212—214° (slight decomp.) (Found : C, 72·2; H, 4·4; N, 4·0. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%), $\lambda_{max.}$ 2150 (ε 17,600), 2430 (ε 38,150), 2560 (ε 37,350), 2770 (ε 51,000), 3240 (ε 14,000), and 3840 Å (ε 3010) in ethanol.

(*b*) A solution of 9-chloro-3 : 4-dihydro-7 : 8-dimethoxy-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridine (0·3 g.) in *p*-cymene (4 c.c.) was refluxed for 7 hr. (oil-bath at 200—210°) with 30% palladium–charcoal (0·15 g.) and a slow stream of hydrogen bubbled through the liquid; hydrogen chloride was steadily evolved. The solution was filtered and the catalyst extracted with *p*-cymene (2 c.c.). On cooling, a colourless solid (m. p. 195—205°) separated. Crystallisation from toluene gave fine needles (100 mg.; m. p. 203—208°), and crystallisation from butanol–2-methoxyethanol yielded colourless plates, m. p. 211—213°, mixed m. p. with the specimen obtained from chelerythrine chloride as under (*a*) 212—214° (Found : C, 71·8; H, 4·6; N, 4·3%). The infrared spectra of the two specimens were identical, and they had the same R_F value (0·87). The compound showed a faint blue fluorescence in dilute alcoholic solution.

7 : 8-*Dimethoxy*-10-*methyl*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridinium Chloride* (III; X = Cl).—A mixture of xylene (10 c.c.) and the tertiary base (XIII) (0·3 g.) was heated to boiling (oil-bath), a few drops of xylene were distilled out to remove traces of water, then dimethyl sulphate (1 c.c.) was added and the mixture refluxed for 40 min., a further 0·3 c.c. of dimethyl sulphate being added after 15 min. An orange-coloured solid rapidly separated from the solution. The mixture was cooled, and the methosulphate collected, washed with benzene and light petroleum (b. p. 40—60°), and dried (300 mg.). The methosulphate was warmed with water, most of the product dissolving, the solution was filtered from a small quantity of insoluble material, left to cool, and again filtered, and a few drops of concentrated hydrochloric acid were added to the filtrate. Fine orange-yellow needles separated. The *chloride*, crystallised from water containing a small quantity of hydrochloric acid, had m. p. and mixed m. p. with chelerythrine chloride 203—205° (decomp.). This m. p. is very sensitive to the rate of heating;

from a bath at 185° chelerythrine chloride has m. p. 207—209° (Found: C, 57·1; H, 5·3. $C_{21}H_{18}O_4NCl,3H_2O$ requires C, 57·5; H, 5·5. Found, after drying at 100° for 2 hr.: C, 62·1; H, 4·9; N, 3·2. $C_{21}H_{18}O_4NCl,H_2O$ requires C, 62·7; H, 5·0; N, 3·5%) (lit.: [13,17] m. p. 210°; 202—203°).

The *ψ*-cyanide formed colourless prisms (from 2-methoxyethanol), m. p. 258—260° (decomp.), mixed m. p. 258—260°: recorded values [13,17,21,22] range from 256° to 263°.

3′ : 4′-*Dihydro*-7 : 8 : 6′ : 7′-*tetramethoxynaphtho*(1′ : 2′-3 : 4)iso*coumarin* (XV).—Phosphoric oxide (2 g.) was dissolved in syrupy phosphoric acid (6 c.c.), and the finely powdered anhydride of α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-dimethoxyphenyl)butyric acid (0·4 g.) was added to the warm solution. The resulting pale yellow solution was heated on a water-bath for 20 min. After 5 minutes' heating a yellow solid started to separate and then the whole solidified. Ice-water was added and the residual gum slowly hardened. The solid was collected, washed with water, ground with sodium carbonate solution, collected, again washed with water, and crystallised from methanol (m. p. 168—169°; 0·36 g.). Two crystallisations from methanol gave the *iso*coumarin as pale, lemon-yellow needles, m. p. 171—172° [Found: C, 68·6; H, 5·6%; *M* (cryoscopic in camphor), 393. $C_{21}H_{20}O_6$ requires C, 68·5; H, 5·4%; *M*, 368], $\lambda_{max.}$ 3340 (ε 24,400), 3470 (ε 26,600), and 3880 Å (ε 12,900). The infrared spectrum contained bands at 1721, 1634, 1605, and 1580 cm.$^{-1}$. The compound was soluble in benzene and acetic acid, insoluble in cold sodium carbonate and sodium hydroxide solutions; it did not give a colour with ferric chloride or 2 : 4-dinitrophenylhydrazine.

The *iso*coumarin may be obtained by heating the free acid with polyphosphoric acid. The product is best isolated by chloroform extraction, the extract being washed with sodium carbonate solution.

2-(2-*Carboxy*-3 : 4-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*oxonaphthalene* (XVI).—The *iso*coumarin (2 g.) was refluxed with a mixture of 2N-aqueous sodium hydroxide (25 c.c.) and ethanol (6 c.c.). After 5 min. all the solid had dissolved; the colourless solution was cooled, diluted with water (20 c.c.), filtered from a trace of insoluble material, and acidified with dilute hydrochloric acid. The resulting *acid* was collected, washed with water, and crystallised from ethanol (1·9 g.). Crystallisation from methanol and then from ethyl acetate gave colourless plates which lost solvent at 135—140°, and had m. p. 176—178° (decomp. to a clear, yellow melt) (Found: C, 65·3; H, 5·8%; equiv., 394. $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·7%; equiv., 386). The 2 : 4-*dinitrophenylhydrazone* formed orange prisms (from 2-ethoxyethanol), m. p. 250—252° (decomp.) (Found: C, 57·2; H, 4·7; N, 9·7. $C_{27}H_{26}O_{10}N_4$ requires C, 57·3; H, 4·6; N, 9·9%).

The keto-acid was heated in an oil-bath at 180° for 5 min.; the resulting yellow glass crystallised when warmed with ethanol, then having m. p. and mixed m. p. with the *iso*coumarin (XV) 170—171°.

7 : 8 : 6′ : 7′-*Tetramethoxynaphtho*(1′ : 2′-3 : 4)iso*coumarin* (XVII).—(*a*) 3′ : 4′-Dihydro-7 : 8 : 6′ : 7′-tetramethoxynaphtho(1′ : 2′-3 : 4)*iso*coumarin (0·3 g.) and 30% palladium–charcoal (70 mg.) were heated together in an atmosphere of hydrogen at 210—220° (metal-bath) for 30 min. Hydrogen was rapidly evolved at 200°. The cold residue was thoroughly extracted with boiling chloroform, the catalyst removed, and the solvent evaporated. The *product* (0·17 g.) formed cream-coloured needles (from dioxan), m. p. 230—231° (Found: C, 68·6; H, 5·1. $C_{21}H_{18}O_6$ requires C, 68·9; H, 4·9%), $\lambda_{max.}$ 2380 (ε 33,700), 2790 (ε 42,400), 3030 (ε 18,600), 3155 (ε 21,200), and 3640 Å (ε 91,400): the infrared spectrum contained bands at 1742, 1629, and 1590 cm.$^{-1}$.

(*b*) A mixture of the acid (XVI) (0·5 g.), chloroform (20 c.c.), and thionyl chloride (5 c.c.) was refluxed for 10 min., and then evaporated *in vacuo* on a water-bath. The resulting yellow solid was heated with ammonia (20 c.c.; *d* 0·88) for 30 min. at 100°, but no change was apparent. The product (0·3 g.) separated from anisole in pale yellow prisms, m. p. 210—230°. A solution of the solid in ether–chloroform (1 : 1) was chromatographed on alumina (acid-washed); elution with ether–chloroform (2 : 1) gave a pale yellow solid, which separated from acetic acid in almost colourless prisms, m. p. 230—231° (softening from 220°) (Found: C, 68·4; H, 4·9%). After crystallisation from dioxan, the material was identical (mixed m. p. and infrared spectrum) with a freshly crystallised specimen of material prepared as under (*a*). The m. p.s of both samples slowly deteriorated.

3′ : 4′-*Dihydro*-7 : 8 : 6′ : 7′-*tetramethoxynaphtho*(1′ : 2′-3 : 4)iso*chromen* (XVIII).—A solution of the *iso*coumarin (XV) (1·0 g.) in warm tetrahydrofuran (30 c.c.) was added to a solution of

[21] Späth and Kuffner, *Ber.*, 1931, **64**, 1123.
[22] Manske, *Canad. J. Res.*, 1943, **21**, 140.

lithium aluminium hydride (0·25 g.) in tetrahydrofuran (12 c.c.). The yellow colour of the *iso*coumarin solution was immediately discharged, and the resulting clear solution was left at room temperature for 2 hr. Excess of hydride was decomposed by a few drops of ethyl acetate, followed by water, and then 2N-sulphuric acid was added. The mixture was extracted with chloroform (3 × 30 c.c.), the extracts were washed with dilute sulphuric acid, water, and dried ($MgSO_4$) and the solvent was removed. Crystallisation of the residue (m. p. 171—174°) from dioxan containing a little ethanol gave colourless, hexagonal plates of the iso*chromen*, m. p. 175—176° (0·73 g.), m. p. unchanged by crystallisation from acetic acid [Found: C, 71·0, 71·4; H, 6·0, 6·4%; *M* (cryoscopic in camphor), 333. $C_{21}H_{22}O_5$ requires C, 71·3; H, 6·2%; *M*, 354], $\lambda_{max.}$ 2480 (ε 11,300) and 3560 Å (ε 19,400); infrared bands were at 1623 and 1603 cm.$^{-1}$. The compound was readily soluble in hot benzene and acetic acid. It contained no active hydrogen and gave negative ferric chloride and 2 : 4-dinitrophenylhydrazine tests. The substance (0·3 g.) was heated with 30% palladium–charcoal (50 mg.) at 200°. Hydrogen was rapidly evolved and the melt solidified; after 20 min. the temperature of the bath was raised to 230° and kept at that temperature for 5 min. The cold melt was extracted with chloroform, the filtered extracts were evaporated, and the residue was digested with methanol (yield, 0·25 g.; m. p. 220—225°). Crystallisation from 2-methoxyethanol gave 7 : 8 : 6′ : 7′-*tetramethoxynaphtho*(1′ : 2′-3 : 4)iso*chromen* as irregular plates, m. p. 225—227° (slight decomp.) (Found: C, 71·5; H, 5·9. $C_{21}H_{20}O_5$ requires C, 71·7; H, 5·7%), $\lambda_{max.}$ 2440 (ε 16,900), 2850 (ε 45,700), 3070 (ε 15,600), and 3240 Å (ε 16,750).

3 : 4-*Dihydro*-7 : 8 : 2′ : 3′-*tetramethoxy*-1 : 2-*benzophenanthridone* (XIX).—3′ : 4′-Dihydro-7 : 8 : 6′ : 7′-tetramethoxynaphtho(1′ : 2′-3 : 4)*iso*coumarin (0·5 g.) was heated for 10 hr. at 150° with ethanol (20 c.c.) which had been saturated with ammonia at −5°. The resulting solid (0·29 g.) was collected and crystallised from butan-1-ol. It formed pale yellow needles, m. p. 259—262°, identical (mixed m. p. and infrared spectrum) with the compound prepared [1] in Part II of this series.

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Dyson Perrins Laboratory, Oxford University. [*Received, July 6th,* 1956.]

873. *The Chemical Synthesis of Polysaccharides. Part I. Synthesis of Gentiodextrins.*

By S. Haq and W. J. Whelan.

When treated with silver oxide in chloroform, 2 : 3 : 4-tri-*O*-acetyl-α-D-glucopyranosyl bromide polymerises with elimination of hydrogen bromide. The products are *O*-acetyl derivatives of levoglucosan and the series of gentiodextrins, *i.e.*, β-glucopyranose polymers based on the repeating 1 : 6-linkage. Molecules containing up to nine glucose units have been detected and the deacetylated products have been characterised by measurement of physical properties and formation of crystalline *O*-acetyl derivatives. Glucose and, probably, cellobiose and ββ-trehalose are also formed. The potentialities of this type of polymerisation are considered.

There are two main methods for the chemical synthesis of polysaccharides. First, a monosaccharide can be caused to undergo condensation polymerisation by being treated with an acid catalyst. For example, glucose heated with hot dilute aqueous acid yields a mixture consisting mainly of disaccharides.[1] Larger polymers can be formed by excluding water from the reaction medium,[2,3,4] thereby limiting the hydrolysis of the polymers. While the yields of the products are appreciable it is not possible to control the reaction

[1] Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309.
[2] Ricketts, *J.*, 1954, 4031.
[3] Kent, *Biochem. J.*, 1953, **55**, 361.
[4] Pacsu and Mora, *J. Amer. Chem. Soc.*, 1950, **72**, 1045.

Products of the polymerisation of 2 : 3 : 4-tri-O-acetyl-α-D-glucopyranosyl bromide

in such a way as to cause the formation of only one type of linkage. Thus Thompson, Anno, Wolfrom, and Inatome [1] obtained *iso*maltose (α-1 : 6-link), gentiobiose (β-1 : 6), maltose (α-1 : 4), cellobiose (β-1 : 4), sophorose (β-1 : 2), nigerose (α-1 : 3),[5, 6, 7] and ββ-trehalose on treatment of glucose with acid. There is, therefore, no control over the position of substitution of the sugar or of the configuration of the linkage, although the 1 : 6-linkage predominates with approximately equal amounts of the α- and β-isomers formed.

The second type of polymerisation leads to linkages of only one type. An example is the Koenigs–Knorr reaction, in which an aldose sugar substituted by halogen at position 1 and with all hydroxyl groups protected, *e.g.*, by esterification, is allowed to react with a second sugar molecule containing only one unprotected hydroxyl group. The elements of hydrogen halide are eliminated, being taken up by a suitable base, *e.g.*, silver oxide or carbonate, and union of the two sugar molecules is usually accompanied by inversion of configuration at $C_{(1)}$ of the halogeno-sugar.[8] Only one product is possible, and by using appropriate reactants di-, tri-, and tetra-saccharides have been synthesised.[8]

It occurred to us that if the halogen atom and the hydroxyl group were present in the same monosaccharide molecule (HO·M·Br) the Koenigs–Knorr reaction might provide a method for the controlled synthesis of a polysaccharide, thus :

$$\text{HO·M·Br} + \text{HO·M·Br} \longrightarrow \text{HO·M·O·M·Br} + \text{HBr, etc.} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It is also possible that an intramolecular elimination of hydrogen halide might occur to form an anhydro-sugar, and this was expected to take place to some extent with the substance used in this investigation, namely, 2 : 3 : 4-tri-*O*-acetyl-α-D-glucopyranosyl bromide,[9] which is prepared by the action of titanium tetrabromide on 2 : 3 : 4-tri-*O*-acetyl-1 : 6-amhydro-α-D-glucopyranose (triacetyl-levoglucosan) and could, therefore, give rise to the parent levoglucosan derivative when treated with silver oxide. Being devoid of free hydroxyl groups, the triacetyl-levoglucosan could not itself be incorporated into an oligosaccharide.

In a preliminary communication [10] we reported the formation from the bromide of the acetates of levoglucosan and a polymeric series of sugars apparently based, as expected, on the β-1 : 6-linkage, *i.e.*, the gentiodextrins. Characterisation of the products was at first based on paper chromatographic evidence. We now report further, more rigid evidence for the nature of these substances.

2 : 3 : 4-Tri-*O*-acetyl-α-D-glucopyranosyl bromide (35 g.) was treated with silver oxide in chloroform at 2—4° for 9 days. Calcium sulphate was added to take up moisture, and iodine was added as a catalyst.[8] The deacetylated products were fractionated on charcoal–Celite and, where necessary, were further purified by paper chromatography and paper ionophoresis. Levoglucosan and oligosaccharides containing up to nine glucose units per molecule were detected and the yields of the di- and tri-saccharides were substantial. The identification of the polymers as gentiodextrins is based on the formation of crystalline acetyl derivatives of the di-, tri-, and tetra-saccharides with the physical properties reported for gentio-biose, -triose, and -tetraose, respectively (see Table); the identification extended to $[\alpha]_D$, molecular weights, and R_P and R_M values of the free sugars. Further, the disaccharide had the same M_G value [11] as gentiobiose, and its hydrolysis by almond emulsin indicated a β-linkage.

From the identification of the di-, tri-, and tetra-saccharides it is assumed that the higher saccharides also belong to the gentiodextrin series. For the penta- and the hexa-saccharide this was confirmed by linear relations between the degree of polymerisation and the following properties of the di- to hexa-saccharides : molecular rotations ($[M]_D$) of the free

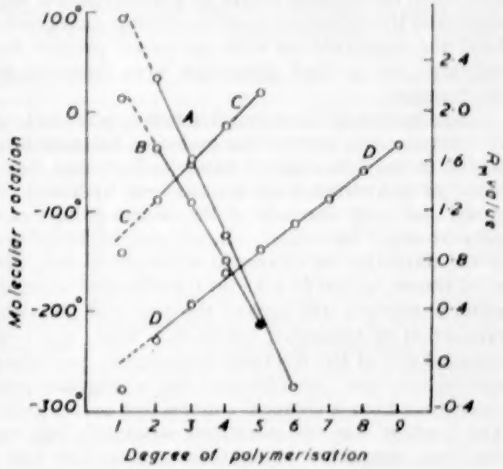
[5] Barker, Bourne, and Stacey, *J.*, 1953, **3084**; Barker, Bourne, and O'Mant, *Chem. and Ind.*, 1955, 425.
[6] Peat, Whelan, and Hinson, *Chem. and Ind.*, 1955, **385**.
[7] Matsuda and Aso, *Tohoku J. Agric. Res.*, 1954, **5**, 123.
[8] Evans, Reynolds, and Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27.
[9] Zemplen and Gerecs, *Ber.*, 1931, **64**, 1545.
[10] Whelan and Haq, *Chem. and Ind.*, 1955, 600.
[11] Foster, *J.*, 1953, 982.

Products of the polymerisation of 2 : 3 : 4-*tri*-O-*acetyl*-α-D-*glucopyranosyl bromide* (35 g.).

Sugar *	Yield † (g.)	$[\alpha]_D$ in H_2O ‡	Mol. wt. Calc.	Found	β-Acetate ‡ M. p.	$[\alpha]_D$ in $CHCl_3$
Glucose	1·41	—	—	—	—	—
Levoglucosan...	1·64	—	—	—	109—110° (110°)	—
Gentiobiose ...	2·10	9·9° (9·5°)	—	—	191—192 (191—192)	− 5·3° (−5·3°)
Gentiotriose ...	3·30	−10·3 (−6·5, −10·6)	504	504	214—215 (211—211·5)	− 9·4 (−7·0)
Gentiotetraose	0·74	−18·4 (−14·5)	666	655	134—135 (134—135)	−12·0 (−10·9)
Gentiopentaose	0·34	−25·9	828	828	230—231	−13·2
Gentiohexaose	0·18	−28·0	—	—	—	—

* Listed in order of emergence from the charcoal–Celite column.
† Calc. from the optical rotations of the fractions eluted from charcoal.
‡ Values from the literature in parentheses. All except that for levoglucosan acetate [9] and the second value for gentiotriose [10] refer to products obtained from pustulan by Lindberg and McPherson.[13]

sugars, $[M]_D$ values of the crystalline acetates (except the hexasaccharide, the acetate of which was not prepared), and R_M values of the sugars (see Figure). These are criteria frequently used for depicting the interrelations of sugars in the same polymeric series.[12, 13, 14]



Molecular rotations and R_M values of the gentiodextrins plotted against degree of polymerisation.

A, $[M]_D$ *values of gentiodextrins.*
B, $[M]_D$ *values of gentiodextrin β-acetates.*
C, R_M *values of gentiodextrins in butan-1-ol–acetic acid–water.*
D, R_M *values in propan-1-ol–ethyl acetate–water.*

The curves are extended by broken lines towards the corresponding values for glucose, which is not, however, to be regarded as the lowest member of the polymeric series; this designation belongs to the disaccharide.[13]

Inclusion of the hepta- to nona-saccharides as members of the gentiodextrin series is based only on R_M values (see Figure) since these substances were present only in small quantity and were not separately isolated.

Thus it is proved that this polymerisation is feasible and, in the case examined, gives the products of lower molecular weight in substantial yields.

In our preliminary communication [10] we mentioned that the formation of a second series of sugars from 2 : 3 : 4-tri-*O*-acetyl-α-D-glucopyranosyl bromide was also detected when the saponified reaction products were fractionated by paper chromatography. The substances constituting the second series were detected on the paper as very faint zones lying between the intense zones corresponding to the gentiodextrins. The R_M values of the second series indicated that the fastest-moving component could have been cellobiose, but the line joining the R_M values was parallel to that for the gentiodextrins, indicating that the main polymeric linkage was probably of the β-1 : 6-type. Fractionation of a large-scale reaction mixture showed that the " impurities " were present only in minute amount. No anomalous product other than the disaccharide was isolated and this only in a yield of 13 mg. (which was probably not all cellobiose; see below), compared with 2·1 g. of gentiobiose. We believe

[12] Whelan, Bailey, and Roberts, *J.*, 1953, 1293.
[13] Lindberg and McPherson, *Acta Chem. Scand.*, 1954, **8**, 985.
[14] French and Wild, *J. Amer. Chem. Soc.*, 1953, **75**, 2612.

that the formation of the cellobiose(?) was probably due to acyl migration in the starting material. It is known that the alkalinity of soda-glass is sufficient to convert 1 : 2 : 3 : 4-tetra-*O*-acetyl-β-D-glucopyranose into the 1 : 2 : 3 : 6-isomers.[15] It seems likely that a similar migration could occur in our triacetyl-bromide, in which case an acetobromo-cellobiose could be formed. This would then react with the starting material, to give acetobromo-derivatives of two trisaccharides, *viz.*, *O*-β-D-glucopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→6)-D-glucopyranose and *O*-β-D-glucopyranosyl-(1→6)-*O*-β-D-glucopyranosyl-(1→4)-D-glucopyranose. These in turn would react with starting material to give tetrasaccharides containing on β-1 : 4- and two β-1 : 6-linkages, but, since the R_M values of the isomers would probably be very similar, paper chromatography of the free sugars would reveal only a single zone in each molecular-weight group. The production of cellotriose and higher cellodextrins is also a possibility, but the amounts would be negligible.

If the polymerisation as defined in reaction (I) were to proceed unhindered then, in theory, the ultimate products would be levoglucosan acetate and a single acetylated molecule of macroscopic dimensions. However, the reaction was observed to have terminated when the average degree of polymerisation was not much greater than three glucose units, and the saponified reaction mixture contained an appreciable quantity of free glucose. That the sugar halides were no longer present was shown by adding methanol to the mixture: no methyl glycosides were detected when the deacetylated products were fractionated.

Termination of the polymerisation appears to be a consequence of the use of silver oxide. Its purpose is to remove the hydrogen bromide formed in the condensation, but this also results in the formation of water (or hydroxyl ions) in such quantity that for every polymeric or anhydro-linkage formed, one hydroxyl group is available to replace a bromo-group and only one-half of the bromo-groups can therefore participate in polymer or anhydro-sugar formation. In addition hydroxyl groups appear at $C_{(1)}$ capable of reacting in the formation of unwanted ββ-trehalose-type polymers. Anhydrous calcium sulphate is, of course, added to take up the liberated water and upon its efficiency in rendering the water unreactive will depend the degree of polymerisation of the oligosaccharides and the proportion of unwanted products. When the synthetic polymers were fractionated on charcoal one of the fractions immediately preceding the gentiobiose had a small negative optical rotation. ββ-Trehalose has a negative rotation ($[\alpha]_D$ −38·2° in H_2O),[16] and its emergence from a charcoal column just before gentiobiose has been noted previously.[16,17] The fraction was not examined separately but was combined with the two succeeding fractions, suspected of containing cellobiose (see above). The mixture was optically inactive, which is consistent with its containing roughly equal quantities of ββ-trehalose and cellobiose ($[\alpha]_D$ +35·2°).[16] The total weight of 13 mg. of disaccharide in these three fractions indicates that although bromo-groups are undoubtedly lost by replacement with hydroxyl, such hydroxyl groups do not offer serious competition to primary hydroxyl groups as acceptors in the polymerisation reaction. We are, nevertheless, seeking means to avoid the production of hydroxyl ions because they are undesirable in that they induce a chain-terminating reaction.

The polymerisation was also studied with the chloro-analogue [9] of our bromide. The formation of levoglucosan, gentiobiose, and gentiotriose was detected by paper chromatography, as for the bromo-compound, but, as expected, reaction was much slower.

Also of interest are the paper-chromatographic observations made on samples of the bromide which had been suspended and warmed gently in saturated barium hydroxide until dissolved. Levoglucosan and gentiobiose were formed in detectable amounts during the few minutes occupied by this treatment.

The polymerisation outlined above may have useful applications. For example, the synthesis is now in progress of what may be called the sophorodextrins, *i.e.*, the β-glucopyranose polymers based on the repeating 1 : 2-linkage. These will provide reference

[15] Helferich and Klein, *Annalen*, 1926, **450**, 219; 1927, **455**, 173.
[16] Peat, Whelan, and Hinson, *Nature*, 1952, **170**, 1056.
[17] Hinson, Ph.D. Thesis, University of Wales, 1953.

compounds for oligosaccharides expected to arise from the crown-gall polysaccharide [18] during linkage analysis.[19] If the final average degree of polymerisation can be increased by avoiding the loss of sugar halide arising as explained above, it should be possible to synthesise polysaccharides for comparison with naturally occurring material, as a test of the validity of the structural analysis of the natural polymers. There is no reason, in theory, why branched polysaccharides should not be synthesised. For this one would require 1-halogeno-sugars containing two or more unsubstituted hydroxyl groups. The degree of branching of such a polymer could be regulated by varying the proportions of halogeno-sugars containing one and more than one free hydroxyl group. Branching in such polymers should be completely random.

Experimental

Preparation of Tri-O-acetyl-levoglucosan.—This was prepared as by Zemplen and Gerecs [9] except that levoglucosan was not isolated in crystalline form, the syrupy distillate (139 g.) from potato starch (300 g.) being acetylated as for the crystalline substance and the product crystallised three times from ethanol and once from hot water: our product (72 g., 24%) had m. p. 110°, $[\alpha]_D$ −50·4° ± 0·6° in EtOH (*c* 0·38; mean of six determinations). Zemplen and Gerecs [9] give m. p. 110°, $[\alpha]_D$ −45·5°. When the compound was left overnight at room temperature in 0·12N-sodium hydroxide, $[\alpha]_D$ changed to −66·3° (neutralised solution). Levoglucosan [9] has $[\alpha]_D$ −66·2°.

Titanium Tetrabromide.—Of the two preparations tried, that utilising the reaction between titanium tetrachloride and hydrogen bromide [20] gave very poor yields. The more satisfactory method employed the reaction between bromine and titanium dioxide.[21] Three 20 g. batches of oxide gave a total of 177 g. of twice-distilled titanium tetrabromide, b. p. 228—230°.

2 : 3 : 4-*Tri-O-acetyl-*α*-*D*-glucopyranosyl Bromide and Chloride.*—Prepared from 25 g. of tri-*O*-acetyl-levoglucosan as by Zemplen and Gerecs,[9] the bromo-compound (18·4 g., 57%) had m. p. 123°, $[\alpha]_D$ +218° in $CHCl_3$ (*c* 0·45; lit.,[9] m. p. 126—127°, $[\alpha]_D$ +217°). The chloro-analogue had m. p. 126—127° (lit.,[9] m. p. 123—124°).

Polymerisation of the Bromo-compound.—(a) *Small scale.* In a typical experiment the bromide (5 g.) was dissolved in alcohol-free chloroform (30 ml.), and anhydrous calcium sulphate (15 g.), silver oxide (3 g.), and iodine (1 g.) were added. There was slight evolution of heat. (When the solids were mixed before adding the solvent the mixture became hot on contact with chloroform.) The flask was fitted with a calcium chloride tube and shaken in the dark at 2—4°. Samples (0·5 ml. each) were removed at daily intervals and centrifuged, and the chloroform was evaporated from the supernatant layer. 0·4N-Barium hydroxide (1 ml.) and 1 drop of phenolphthalein were added and the mixture gently warmed in a water-bath for 1 min. Thereafter the alkali was added dropwise until the pink colour persisted for 5 min. Barium ions were then removed as barium sulphate, and the supernatant solution was applied to paper chromatograms which were irrigated in one or both of the solvent systems butan-1-ol–acetic acid–water (4 : 1 : 5, by vol.) and propan-1-ol–ethyl acetate–water (6 : 1 : 3, by vol.).

The chromatograms were developed with alkaline silver nitrate [22] to detect reducing and non-reducing sugars and benzidine–trichloroacetic acid [23] for reducing sugars only. After 24 hours' reaction the deacetylated mixture contained sugars corresponding, in order of decreasing R_F value, to levoglucosan, glucose, and gentio-biose, -triose, and -tetraose. Gentio-pentaose became detectable after 48 hr. and the hexaose after 72 hr. Thereafter, up to 11 days, no products of higher molecular weight were detected. However, increasing quantities of the chloroform-soluble material became very difficultly soluble in aqueous barium hydroxide, even when warmed. The insoluble residue, when deacetylated in 50% aqueous-ethanolic sodium hydroxide, proved to be a mixture of the three- to six-membered gentiodextrins.

(b) *Large scale.* The bromide (35 g.) in dry ethanol-free chloroform (150 ml.) was treated with anhydrous calcium sulphate (50 g.), silver oxide (18 g.), and iodine (1 g.) for 9 days at 2—4° as above. Silver oxide (10 g.) and dry methanol (20 ml.) were added and after being shaken overnight the filtered solution was evaporated under reduced pressure, leaving a syrup (27·6 g.). This was dissolved in methanol (600 ml.), and 0·6N-barium methoxide (50 ml.) was

[18] Putman, Potter, Hodgson, and Hassid, *J. Amer. Chem. Soc.*, 1950, **72**, 5024.
[19] Peat, Whelan, and Edwards, *J.*, 1955, 355.
[20] Olsen and Ryan, *J. Amer. Chem. Soc.*, 1932, **54**, 2215.
[21] Baxter and Butler, *J. Amer. Chem. Soc.*, 1928, **50**, 408.
[22] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[23] Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114.

added. After 48 hr. at 0° the solution was neutralised with aqueous 3N-hydrochloric acid and evaporated. The residue, dissolved in a minimum of water, was added to a charcoal–Celite column [23] (1 : 1 by wt.; 160 × 5 cm.) and fractionated by gradient elution.[24] A reservoir of water (20 l.), some 8 ft. above, led to the top of the column and the level in the reservoir was maintained by a constant-head device feeding in 50% aqueous ethanol. Fractions (approx. 500 ml. each) were collected automatically and the rotation of each was measured in a 4 dm. tube after filtration. The curves relating optical rotation to fraction no. were plotted and the fractions constituting each node of optical activity were combined. The optical rotation returned to zero between all nodes from glucose to gentiopentaose, except between levoglucosan and gentiobiose, which were separated by three fractions (nos. 15—17) containing cellobiose(?) and ββ-trehalose(?) (see below). Glucose was found in fractions 5—7, levoglucosan in 10—16, and gentio-biose in 18—21, -triose in 27—33, -tetraose in 39—47, -pentaose in 49—57, and -hexaose in 58—75. After fraction 75 had been collected 50% aqueous ethanol was applied to the column and a further 25 fractions were collected and combined. The eluates were evaporated to dryness under reduced pressure. The solutions containing the di- to hexa-saccharides were examined by paper chromatography to determine the carbohydrate purity of the fractions. The gentiobiose contained a trace of cellobiose and the triose-to-hexaose fractions were each contaminated with traces of the next lower member of the series. Some or all of each fraction except the tetrasaccharide was purified by partition chromatography on Whatman No. 3 paper (80 mg. of sugar per sheet 18¼ × 22½ in.) in butan-ol–acetic acid–water. The products eluted from the papers by water were evaporated to dryness under reduced pressure, dissolved in known volumes of water, and filtered to remove cellulose fibre. Sufficient tetrasaccharide occurring as impurity in the pentasaccharide fraction was obtained to carry out the measurements of $[\alpha]_D$ and molecular weight of the free sugar (see below). The main tetrasaccharide fraction was reserved for acetylation (see below). As a precaution against the contamination of the gentiotriose by trisaccharides containing 1 : 4- or trehalose-type linkages, formed in side reactions, which might not be separable by partition chromatography but should be separable by ionophoresis, the gentiotriose was placed on sheets of Whatman No. 3 paper (200 mg. of sugar per sheet 18¼ × 22½ in.) and subjected to ionophoresis for 24 hr. as described below. The recovered sugar was freed from borate by addition of the acidified aqueous solution (hydrochloric acid to pH 5) to a small charcoal–Celite column (1 : 1, w/w), elution of the borate with water and of the trisaccharide with 50% aqueous ethanol, then evaporation to dryness, and dissolution in water.

Characterisation of the Products of Polymerisation.—The oligosaccharide solutions were treated with Somogyi's deproteinising reagents [25] to remove substances interfering with reductometric measurements [13] and were then examined for the following properties.

(a) *Specific optical rotation.* Portions of the solutions were hydrolysed in 1·5N-sulphuric acid for 4 hr. at 100° and the oligosaccharide concentrations determined by measurement of the glucose liberated.[26] The optical rotations were measured in a 4 dm. tube and the $[\alpha]_D$ values calculated (see Table). Values for the molecular rotation ($[M_D]$) were calculated from molecular weights assumed from the formula $(C_6H_{10}O_5)_n - (n-1)H_2O$, where n is the degree of polymerisation (see Figure).

(b) *Molecular weight.* A preliminary experiment showed that gentiopentaose developed maximum reducing power during 30 minutes' heating with Somogyi's copper reagent,[27] the same time as required for gentiobiose. This behaviour parallels that of the *iso*maltodextrins [28] and contrasts with that of the maltodextrins [13] in which series the time of heating increases progressively with molecular weight. The reducing equivalent of each of the oligosaccharides from the biose to the pentaose was determined and, a molecular weight of 342 being assumed for the biose, that of each of the higher saccharides was calculated on the assumption of one reducing group per molecule (see Table).

(c) R_F *value.* The R_F values of glucose and the di- to hexa-saccharides were determined in the two solvents mentioned above. The values for the hepta- to nona-saccharides were measured on the material eluted from the charcoal column by 50% ethanol. R_F values were converted into R_M values [13] and are plotted in the Figure.

[24] Alm, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826; Alm, *ibid.*, p. 1186.
[25] Somogyi, *J. Biol. Chem.*, 1945, **160**, 69.
[26] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.
[27] Somogyi, *J. Biol. Chem.*, 1945, **160**, 61.
[28] Turvey and Whelan, *Biochem. J.*, in the press.
[29] Edwards, Ph.D. Thesis, University of Wales, 1955.

(d) M_G *values.* These were measured on samples of sugars subjected to ionophoresis on Whatman No. 54 paper in 0·2M-borate buffer (pH 8·7) at 9 v/cm. for 18 hr.

(e) *Sugar acetates.* Dried samples of levoglucosan and the di- to penta-saccharides were separately acetylated with sodium acetate–acetic anhydride, and the products worked up in the usual way and crystallised to constant m. p. $[M]_D$ values were calculated from the measured $[\alpha]_D$ value and the assumed molecular weight, as for the free sugar (see above). Elementary analyses of the acetates were done for the disaccharide (Found: C, 49·5; H, 5·8. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6%), trisaccharide (Found: C, 49·8; H, 5·8. Calc. for $C_{40}H_{54}O_{27}$: C, 49·7; H, 5·6%), tetrasaccharide (Found: C, 49·1; H, 5·7. Calc. for $C_{52}H_{70}O_{35}$: C, 49·8; H, 5·6%), and for *gentiopentaose heptadeca-O-acetate* (Found: C, 50·3; H, 5·3. $C_{64}H_{86}O_{43}$ requires C, 49·8; H, 5·6%).

Minor Products of the Polymerisation Reaction.—When examined by paper chromatography, fractions 15—17 from the large-scale polymerisation (see above) migrated as a single spot occupying the position of cellobiose and reducing the benzidine reagent (N.B. ββ-trehalose has almost the same R_F value as cellobiose [17]). The M_G value of the material was that of cellobiose. The carbohydrate content of the fractions was measured as for the gentiodextrins (see above).

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874. *The Chemistry of Santonin. Part III.* The Stereochemistry of Some Reduction Products of Santonin.*

By Wesley Cocker and T. B. H. McMurry.

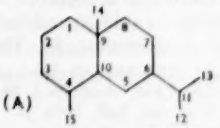
Absolute configurations, which differ from those suggested by Yanagita and Tahara,[1] are assigned to the known tetrahydrosantonins. Several hexahydrosantonins have been prepared.

Recently three papers [1,2,3] have focused attention on the hydrogenation products of santonin (I). Early workers [4] recorded the preparation of two of the four possible tetrahydrosantonins, the so-called α-isomer, m. p. 155—156°, and the β-isomer, m. p. 105°. Yanagita and Tahara [1] recently described the reduction of santonin in acetone over palladised charcoal, and the isolation of α-tetrahydrosantonin and two other tetrahydro-compounds. One of these, m. p. 143—144°, a new compound, was confusingly named the β-isomer, whilst the other, m. p. 96—97°, which we believe to be substantially identical with the β-isomer of earlier workers, was named the γ-isomer. The isomer, m. p. 143—144°, could be converted into α-tetrahydrosantonin by treatment with mineral acid, and hence was assumed to have an axial methyl group at $C_{(4)}$. The γ-isomer is unaffected by acid.

Kovács, Herout, Horák, and Sorm [2] reduced santonin over a palladium–barium carbonate catalyst in methanol and obtained α-tetrahydrosantonin, which they renamed 3-ketosantan-5 : 12-olide-a,† and an isomeric compound, 3-ketosantan-5 : 12-olide-b,

* Part II, *J. Pharm. Pharmacol.*, 1956, in the press.

† The numbering used by Kovács *et al.* is as shown in (A) and differs from our convention (I).



(A)

[1] Yanagita and Tahara, *J. Org. Chem.*, 1955, **20**, 959.

[2] Kovács, Herout, Horák, and Sorm, *Chem. Listy*, 1955, **49**, 1856; *Coll. Czech. Chem. Comm.*, 1956, **21**, 225.

[3] Tahara, *J. Org. Chem.*, 1956, **21**, 422.

[4] Simonsen, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 256; Weinhaus and von Oettingen, *Annalen*, 1913, **397**, 219; Weinhaus, *Ber.*, 1913, **46**, 2839; Wedekind and Beniers, *Annalen*, 1913, **397**, 246; Asahina, *Ber.*, 1913, **46**, 1775.

m. p. 103—105°, believed to be identical with the β-isomer of earlier workers.[4] A third tetrahydro-compound, 3-ketosantan-5 : 12-olide-c, m. p. 145—146°, was obtained by oxidation of the hexahydrosantonin, 3-hydroxysantan-5 : 12-olide-c, formed by reduction of santonin over a platinum catalyst in methanol. This tetrahydrosantonin was isomerised by mineral acid to 3-ketosantan-5 : 12-olide-a, and hence is probably identical with the β-tetrahydrosantonin of the Japanese workers.

Yanagita and Tahara [1] conclude that their α- and β-isomers have *cis*-A/B ring-fusion, whilst their γ-isomer is *trans*-fused. These assignments are based upon a comparison of the molecular rotations of the α- and the γ-isomer with the *cis*- and *trans*-A/B ring-fused steroidal 3-ketones, and on the fact that, like corresponding *cis*- and *trans*-A/B fused steroids, the α-isomer gives a 2 : 4-dibromo-derivative whilst the γ- gives a 2 : 2-dibromo-derivative, which rearranges to the 2 : 4-isomer. The latter argument is of doubtful value. In a recent paper,[3] Tahara has shown that the keto-acid (II) derived from the so-called γ-tetrahydrosantonin equilibrates at $C_{(5)}$ (our numbering) with alkali to a mixture containing a predominating quantity of the keto-acid derived from α-tetrahydrosantonin, the latter thus appearing to have the more stable *trans*-decalin system.

Our own investigations support this revision. We have related the three tetrahydrosantonins, and the hydroxy-acid corresponding to the fourth, to six of the eight possible hexahydrosantonins; considerations of molecular rotations and of the known stereochemical course of reductions enable structures to be assigned to the hexa- and hence to the tetra-hydrosantonins.

In this paper we employ the nomenclature suggested by Cocker and Cahn,[5] which avoids trivial names and gives a rigid description of the compounds in question. The alternative names previously given to these compounds are set out in Table 1. It is now known [6,7,8,9] that santonin has the absolute configuration shown in (I). Eudesmol,[10] carissone,[11] and α-cyperone [12] have the same configuration at $C_{(7)}$ and $C_{(10)}$.

TABLE 1. *Alternative names used for the reduced santonins.*

Present authors	Yanagita and Tahara	Kovács *et al.*	Earlier workers
3-Oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII)	α-Tetrahydrosantonin	3-Ketosantan-5 : 12-olide-a	α-Tetrahydrosantonin
3-Oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV)	γ-Tetrahydrosantonin	3-Ketosantan-5 : 12-olide-b	β-Tetrahydrosantonin
3-Oxo-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (VII)	β-Tetrahydrosantonin	3-Ketosantan-5 : 12-olide-c	—
3α-Hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV; R = H)	—	3-Hydroxysantan-5 : 12-olide-c	—
3β-Hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III)	—	3-Hydroxysantan-5 : 12-olide-b	—

(A) *Compounds having* trans-A/B *Ring-fusion.*—We have found that when santonin was hydrogenated in acetic acid over a platinum catalyst a compound believed to have the *cis*-A/B ring-fusion, 3β-hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide [2,13] (III), discussed below, was obtained in low yield and a mixture from which, by acetylation, 3α-acetoxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV; R = Ac) was obtained in good yield. Hydrolysis gave the alcohol (IV; R = H), which was obtained in two crystalline forms; the higher-melting form is probably identical with 3-hydroxysantan-5 : 12-olide-c. The negative shift in molecular rotation on acetylation and the negative molecular-rotation contribution of the hydroxyl group (Table 2) indicate, according to the rule of Klyne and Stokes,[14] that the hydroxyl is α-orientated. The conditions of reduction make it

[5] Cocker and Cahn, *Chem. and Ind.*, 1955, 384; Cocker and McMurry, *J.*, 1955, 4430.
[6] Bruderer, Arigoni, and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858.
[7] Chopra, Cocker, and Edward, *Chem. and Ind.*, 1954, 41.
[8] Abe and Sumi, *ibid.*, 1955, 253.
[9] Corey, *J. Amer. Chem. Soc.*, 1955, **77**, 1044.
[10] Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 313.
[11] Barton and Tarlton, *J.*, 1954, 3492; Ayer and Taylor, *J.*, 1955, 3027.
[12] Howe and McQuillin, *J.*, 1955, 2423.
[13] Ruzicka and Eichenberger, *Helv. Chim. Acta*, 1930, **13**, 1117.
[14] Klyne and Stokes, *J.*, 1954, 1979; Stokes and Bergmann, *J. Org. Chem.*, 1952, **17**, 1194; Mills, *Chem. and Ind.*, 1953, 218; Barton and Holness, *J.*, 1954, 4665.

probable that the hydroxyl group is axial and hence the rings A/B are *trans*-fused; this involves 1 : 2-α-addition of hydrogen to the Δ^4-double bond and consequently an axial 4-methyl group. Catalytic hydrogenation of 3-keto-Δ^4-steroids usually gives the *cis*-decal-3-one system,[15] but cases are known where the *trans*-decal-3-one system is obtained.

TABLE 2.

Compound	$[M]_D$ of alcohol	$[M]_D$ of acetate	$[M]_D$ of corresponding deoxy-compound [a]	ΔOH [b]	Δ_1 [b]
3β-Hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III)	− 21°	+ 96°	− 64°	+ 43°	+117°
3α-Hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV; R = H)	+ 91	+ 45	+218	−127	− 46
3α-Hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (X; R = H)	+ 42	− 83	+ 63	− 21	−125
3β-Hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XI; R = H)	+128	+186	+ 63	+ 65	+ 58
3α-Hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XVI)	− 96	− 94	− 64	− 32	+ 2
3β-Hydroxy-4 : 11α(H),5 : 6β(H)-eudesman-6 : 13-olide (XIX)	+ 92	+208	—	—	+116

TABLE 3.

Compound	$[M]_D$ of chloro-compound	$[M]_D$ of corresponding dechloro-compound	ΔCl
3α-Chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XII)	−60°	+63°	−123°
3β-Chloro-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XVIII)	+83	−64	+147

[a] From Kovács *et al.*[2] [b] ΔOH and Δ_1 are defined as suggested by Klyne and Stokes.[14]

Treatment of the hexahydrosantonin (IV; R = H) with phosphorus oxychloride and pyridine gave a mixture of 4 : 5 : 11α(H),6β(H)-eudesm-2-en-6 : 13-olide (V) and 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI). The 3 : 4-position of the double bond in the latter compound follows from its infrared absorption at 1774 (lactone) and 851 cm.$^{-1}$ (trisubstituted olefin), and from its ozonolysis to a gummy product exhibiting peaks at 2790 (aldehyde), 1779 (lactone), and 1721 cm.$^{-1}$ (carbonyl), and giving positive Schiff's and Tollens's tests and a positive iodoform reaction. The gummy product from the ozonolysis of the other olefin (V), on the other hand, gave tests for aldehyde groups but no iodoform, showing it to be the Δ^2-isomer.

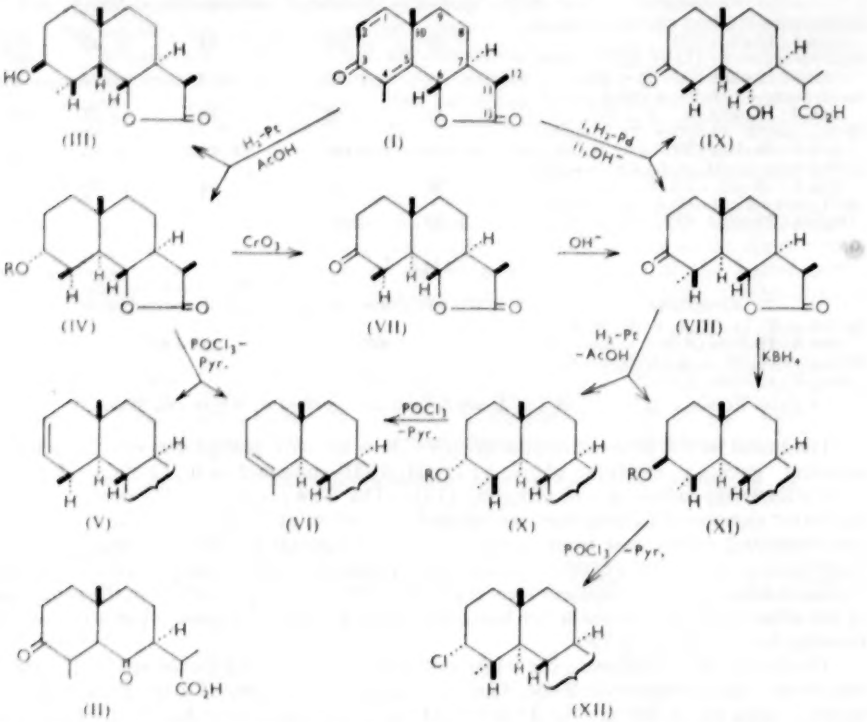
The factors which influence the relative stability of the 2- and 3-enes are (*a*) the *trans*-ring fusion which favours the 2-ene,[16] and (*b*) the greater stability of a tri- than a di-substituted olefin which favours the 3-ene.[17] The former would be the kinetically controlled product on account of diaxial elimination [18] of water from the alcohol (IV). The formation of the 3-ene indicates at least some dehydration by a carbonium-ion mechanism.

Oxidation of the hexahydrosantonin (IV) affords the known tetrahydrosantonin (VII; Table 1), which is epimerised at $C_{(4)}$ by alkali to 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII; Table 1). These ketones must accordingly have *trans*-fused A/B rings. The carbonyl stretching frequency of both occurs at 1703 cm.$^{-1}$, the configuration of the 4-methyl group having no effect.[19]

The ketone (VIII) may also be obtained by hydrogenation of santonin in acetone over palladised charcoal and treatment of the product with alkali;[4] a second compound formed in smaller yield is shown later to have the formulation (IX). These compounds arise from α- and β-addition respectively of hydrogen to the 4 : 5-double bond and subsequent epimerisation at $C_{(4)}$.

[15] Halder, *Experientia*, 1955, **11**, 175; Lewis and Shoppee, *J.*, 1955, 1365.
[16] Taylor, *Chem. and Ind.*, 1954, 250; Dreiding, *ibid.*, p. 1419.
[17] Ingold, "Structure and Reactivity in Organic Chemistry," Cornell Univ. Press, Ithaca, 1954, p. 468—472.
[18] Grand and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 344; Berner, Lardon, and Reichstein, *ibid.*, 1947, **30**, 1542.
[19] Cf. Lukes, Poos, Beyler, Johns, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 1707; Braude and Waight, "Progress in Stereochemistry," Butterworths, London, 1954, Vol. I, p. 170 (ed. Klyne).

When the ketone (VIII) was reduced with potassium borohydride it gave a good yield of 3β-hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XI; R = H), which on acetylation showed a positive shift in molecular rotation and must therefore have a β-hydroxyl group,[14] which from the method of preparation must also be equatorial. Reaction of this alcohol (XI; R = H) with phosphorus oxychloride and pyridine afforded 3α-chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XII), the α-orientation of the chlorine following from its negative molecular-rotation contribution [14] (Table 3). This reaction involves an



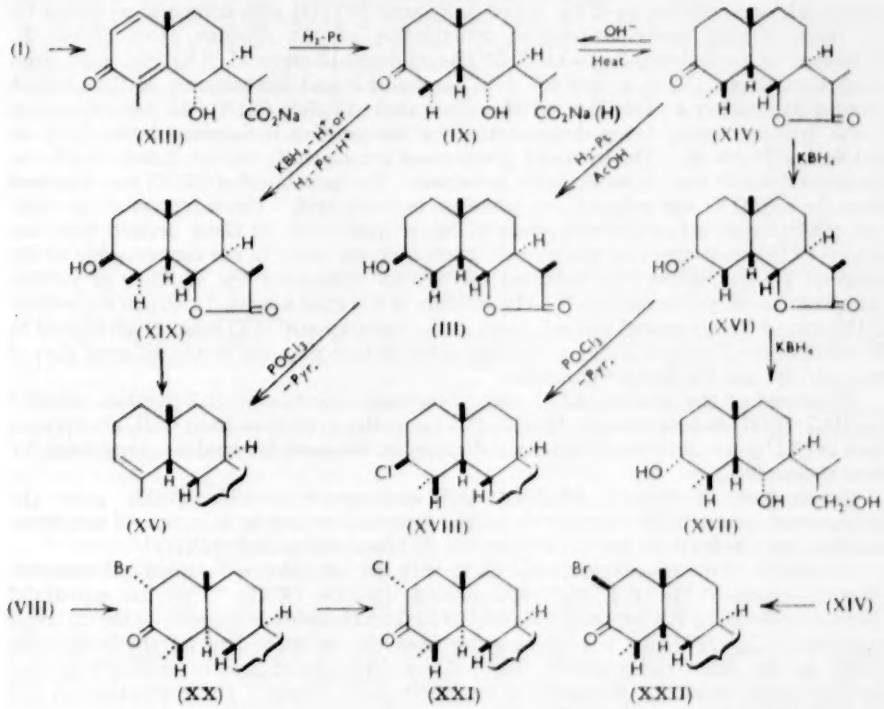
S_N2 replacement with inversion, analogous to the similar reaction of sterols with phosphorus pentachloride.[20] *

Hydrogenation of the ketone (VIII) with platinic oxide in acetic acid and acetylation of the product gave a mixture of the acetate (XI; R = Ac) and of a new acetate, 3α-acetoxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (X; R = Ac). The latter on alkaline hydrolysis gave the corresponding 3α-alcohol (X; R = H). The negative shift in molecular rotation on acetylation of the alcohol and the negative molecular-rotation contribution of the hydroxyl group (Table 2) show [14] that the latter is α-orientated and hence axial. Reaction of the alcohol (X; R = H) with phosphorus oxychloride and pyridine gave a complex of the corresponding 3 : 4-unsaturated and 3-chloro-compounds from which by chromatography on alumina 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI) was obtained in a pure condition. The formation of the latter is to be expected of the alcohol (X) : the formation of the chloro-compound is surprising.

* Fieser, Fieser, and Chakravarti (*J. Amer. Chem. Soc.*, 1949, **71**, 2226) have recorded the replacement of an equatorial hydroxyl group by chlorine using phosphorus oxychloride in pyridine. They suggest that no inversion occurs, because the product is stable in boiling pyridine. The same conversion, however, can be carried out by using phosphorus pentachloride (Wintersteiner and Moore, *ibid.*, 1943, **65**, 1507), a reaction known to cause inversion (Shoppee, *J.*, 1946, 1138).

[20] Shoppee, *J.*, 1946, 1138.

(B) *Compounds having a* cis-A/B *Ring-fusion.*—When sodium santoninate (XIII) was hydrogenated over platinum black in aqueous solution [21] it gave the *cis*-A/B-fused keto-acid (IX), also obtained (see above) by the direct hydrogenation of santonin. The acid can be lactonised either by heating [4] or with toluene-*p*-sulphonic acid in acetic acid,[2] to give 3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV), this reaction being reversed by treatment



of the lactone with alkali. The axial configuration of the 4-methyl group in the ketone (XIV) is required since on hydrogenation in acetic acid over platinum it gave 11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III), which as mentioned above can also be obtained, in low yield, by hydrogenation of santonin under the same conditions. In the latter case, the 1 : 2-β-addition of hydrogen to the double bond requires the 4- and the 5-hydrogen atom to be *cis* with respect to each other, and hence the 4-methyl to be axial. 1 : 4-Addition of hydrogen to the enone system could lead to the equatorial configuration for the 4-methyl group: this is regarded as less likely, since 1 : 2-addition, to give the *trans*-A/B-fused hexahydrosantonin (IV), in which the 4-methyl group is known to be axial, has already been demonstrated (IV ⟶ VII ⟶ VIII).

Dehydration of the alcohol (III) with phosphorus oxychloride in pyridine gave 11α(H),5 : 6β(H)-eudesm-3-en-6 : 13-olide (XV). This is an unexpected *cis*-elimination, and it is significant that none of the 2-ene, arising from the normal *trans*-diaxial elimination, was formed. Of the two 3-enes, (VI) and (XV), the former is the more dextrorotatory, as would be expected from a comparison with the corresponding 3-methyl*cyclo*hexenes.[22]

Ozonolysis of the olefin (XV) gave a gum with the properties of an aldehyde and a methyl ketone. In the infrared spectrum it exhibited peaks at 2780 (aldehyde), 1785 (lactone), and 1730—1766 cm.$^{-1}$ (carbonyl).

[21] Cusmano, *Atti R. Accad. Linceі*, 1913, V, **22**, 507.
[22] Mills, *J.*, 1952, 4976.

Reduction of 3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV) with a slight excess of potassium borohydride gave the equatorial alcohol, 3α-hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XVI). The molecular-rotation shift on acetylation of this alcohol (Table 2) is very small and has no diagnostic value. When the reduction was performed with a large excess of borohydride, the lactone ring was also reduced, thus affording the triol (XVII). Reaction of the alcohol (XVI) with phosphorus oxychloride and pyridine gave the chloro-compound (XVIII) with inversion, as shown by the large positive molecular-rotation contribution of the chlorine atom (Table 3). Reduction of 6α-hydroxy-3-oxo-4α(H),5β(H)-eudesman-13-oic acid (IX) [the acid from which the lactone (XIV) is derived] with borohydride and lactonisation of the product afforded 3β-hydroxy-4 : 11α(H),5 : 6β(H)-eudesman-6 : 13-olide (XIX), the β-configuration of the hydroxyl group being demonstrated by the positive molecular-rotation shift on acetylation (Table 2). The hydroxyl group must consequently be orientated axially, an unexpected result from a borohydride reduction. The same alcohol (XIX) was obtained when the acid (IX) was reduced over platinum in acetic acid. The reduction of the keto-acid (IX) to give a hexahydrosantonin, different from either of those derived from the lactone (XIV), indicates that the former differs from the latter in the configuration of the 4-methyl group. Klyne has discussed the factors influencing the stability of various configurations of *cyclo*hexanones.[23] The stability of tne axial 4-methyl group in the lactone (XIV) and of the equatorial methyl group in the hydroxy-acid (IX) must be attributed to the effect of the release of strain on opening of the lactone ring, and to the different sizes of the hydroxyl and the lactone groupings.

Treatment of the alcohol (XIX) with phosphorus oxychloride and pyridine afforded 11α(H),5 : 6β(H)-eudesm-3-en-6 : 13-olide (XV) in better yield than from (III), as expected since in (XIX) the elements of water are disposed in the most favourable arrangement for their elimination.

Bromination of 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) gave the 2α-bromo-compound (XX), having equatorial bromine,[1] whilst bromination of the corresponding *cis*-A/B-fused ketone (XIV) gave the 2β-bromo-compound (XXII).[1]

Treatment of the bromo-compound (XX) with lithium chloride in dimethylformamide gave 2-α-chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XXI). This has equatorial chlorine as shown by the hypsochromic shift of 15 Å and increase in intensity of the carbonyl maximum ($\lambda_{max.}$ 2775, log ε 1·53) in going from the corresponding tetrahydrosantonin (VIII) to the chloro-compound.[25] The halogen replacement is very probably an S_N1 reaction which would be favoured by the highly polar solvent : the alternative, an S_N2 reaction followed by inversion, is less likely.

Experimental

Ultraviolet spectra were measured for EtOH solutions with a Beckman DU instrument, and the infrared spectra in $CHCl_3$ with a Hilger 800 double-beam instrument. $[\alpha]_D$ refer to $CHCl_3$ solutions unless otherwise stated.

Hydrogenation of Santonin at a Platinum Catalyst.—Santonin (5·0 g.) in acetic acid (150 c.c.) was stirred with platinic oxide catalyst (0·2 g.) in hydrogen for 5 hr. After removal of the catalyst and solvent, the product was treated with ether (50 c.c.). The undissolved solid was collected and recrystallised from ethanol, to give 3β-hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III) (0·46 g.) as needles, m. p. 210—212°, $[\alpha]_D^{16}$ −8·5° (*c* 0·77) (Found : C, 71·7; H, 9·5. Calc. for $C_{15}H_{24}O_3$: C, 71·5; H, 9·6%). Ruzicka and Eichenberger [13] record m. p. 210—211°; Kovács *et al.*[3] give m. p. 213—215°, $[\alpha]_D$ −8·5°, for 3-hydroxysantan-5 : 12-olide-b.

The ethereal solution was evaporated and the residue was heated on a water-bath with pyridine (5 c.c.) and acetic anhydride (5 c.c.). Removal of the solvents gave *3α-acetoxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide* (IV; R = Ac, 4·0 g.) as needles (from ethanol), m. p. 199—200°, $[\alpha]_D^{20}$ +15·4° (*c* 0·72) (Found : C, 69·4; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

[23] Klyne, *Experientia*, 1956, **12**, 119.
[24] Holysz, *J. Amer. Chem. Soc.*, 1953, **75**, 4432.
[25] Cookson, *J.*, 1954, 282.

3α-Hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV; R = H).—The preceding compound (2·0 g.) was refluxed for 2 hr. with potassium hydroxide (1·0 g.) in methanol (50 c.c.). The product obtained on acidification was *3α-hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide* (IV; R = H) (1·55 g.), forming fine needles (from alcohol), m. p. 108—110°, $[\alpha]_D^{20}$ +36·0° (*c* 0·95) (Found: C, 71·0; H, 9·8. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). On one occasion, a second crystalline modification (also needles), m. p. 130—131°, was obtained. Kovács *et al.*[3] record m. p. 135°, $[\alpha]_D$ +42·7°, for 3-hydroxysantan-5 : 12-olide-c.

Action of Phosphorus Oxychloride in Pyridine on 3α-Hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV).—A mixture of the above hydroxy-compound (IV) (5 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·75 c.c.) was set aside at room temperature for 24 hr. The solid obtained on dilution with water was collected, dried, and extracted with boiling light petroleum (b. p. 60—80°). Chromatography of the extract on "Woelm" brand acid alumina gave *5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide* (VI) (0·27 g.) as plates, m. p. 136—137°, $[\alpha]_D^{20}$ +90·6° (*c* 0·13) (Found: C, 77·3; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%), and *4 : 5 : 11α(H),6β(H)-eudesm-2-en-6 : 13-olide* (V) (0·21 g.) as plates, m. p. 107—108°, $[\alpha]_D^{21}$ +98·0° (*c* 0·55) (Found: C, 77·0; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

Ozonolysis of 4 : 5 : 11α(H),6β(H)-Eudesm-2-en-6 : 13-olide (V).—Excess of ozone was passed into a solution of the unsaturated compound (V) (1·0 g.) in methyl acetate (30 c.c.). Hydrogenation of the ozonide over 10% palladised charcoal (0·2 g.) gave an oil which rapidly restored the colour to Schiff's reagent and reduced Tollens's reagent. It failed to give iodoform with sodium hypoiodite.

Ozonolysis of the isomer (VI) in a similar manner gave a gum which gave iodoform with sodium hypoiodite, reduced Tollens's reagent, and restored the colour to Schiff's reagent.

3-Oxo-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (VII).—A mixture of 3α-hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV) (0·52 g.), chromium trioxide (0·14 g.), and acetic acid (30 c.c.) was set aside for 3 days at room temperature. Removal of the acetic acid gave 3-oxo-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide as fine needles, m. p. 141—142° (from aqueous ethanol), $[\alpha]_D^{16}$ +71·5° (*c* 0·64) (Found: C, 71·3; H, 8·9. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9%). Yanagita and Tahara[1] record m. p. 143—144°, $[\alpha]_D$ +64·5°, for β-tetrahydrosantonin; Kovács *et al.*[2] give m. p. 145—146°, $[\alpha]_D$ +77·5° for 3-oxosantan-5 : 12-olide-c.

3-Oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) *from 3-Oxo-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide* (VII) (cf. refs 1, 2).—The ketone (0·10 g.) was heated on the water-bath for 15 min. with sodium hydroxide (0·5 g.) in water (10 c.c.), and the solution was then acidified. The product was 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) (0·07 g.), m. p. and mixed m. p. 152—153° (see below).

Hydrogenation of Santonin in Acetone over Palladised Charcoal.—(a) *3-Oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide* (VIII). Santonin (25 g.) and 10% palladised charcoal (2·5 g.) in acetone (300 c.c.) were shaken for 24 hr. in an atmosphere of hydrogen. The resulting solid was dissolved by heating it with 10% sodium hydroxide solution. The mixture was filtered. The product formed on acidification of the filtrate was recrystallised several times from ethanol, to give 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (12·2 g.), m. p. 154—155°, $[\alpha]_D^{18}$ +27·9° (*c* 2·1).

(b) *6α-Hydroxy-3-oxo-4α(H),5β(H)-eudesman-13-oic acid* (IX).—The mother-liquors from which the ketone (VIII) was deposited were combined, evaporated to a small bulk, and treated with ethanol (100 c.c.) containing potassium hydroxide (2·5 g.). The solid potassium salt was collected, washed with ethanol, dissolved in water, and acidified. The resulting solid was recrystallised from aqueous ethanol, to give 6α-hydroxy-3-oxo-4α(H),5β(H)-eudesman-13-oic acid (IX; see also below) (1·4 g.), m. p. 191—192°, $[\alpha]_D^{19}$ +2·2° (*c* 1·16 in MeOH). Cusmano[21] records m. p. 190°, $[\alpha]_D^{19}$ +2°. Kovács *et al.*[2] record m. p. 190—192°, $[\alpha]_D$ +20·7°, for 3-keto-5-hydroxysantanic acid-b.

Hydrogenation of 3-Oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) *at a Platinum Catalyst.*—A mixture of the ketone (2·5 g.), platinic oxide (0·1 g.), and acetic acid (30 c.c.) was stirred in hydrogen for 2 hr. The resulting mixture of alcohols was heated with acetic anhydride (10 c.c.) and pyridine (10 c.c.) on the water-bath for 1 hr. Fractional crystallisation of the product from ethyl acetate–light petroleum (b. p. 60—80°) gave *3α-acetoxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide* (X; R = Ac) (0·7 g.) as rhombs, m. p. 153—154°, $[\alpha]_D^{17}$ −28·3° (*c* 0·7) (Found: C, 69·5; H, 8·8. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%), and 3β-acetoxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XI; R = Ac) (1 g.), m. p. 143° undepressed by a sample prepared by the alternative method given below.

3α-Hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (X; R = H).—The corresponding

acetate (0·4 g.) was refluxed for 1·5 hr. with a solution of potassium hydroxide (0·2 g.) in methanol (20 c.c.), and the solution then acidified. The product, **3α-*hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide*** (X; R = H) (0·24 g.) was obtained as needles (from ethanol), m. p. 142—143°, $[\alpha]_D^{25}$ +16·6° (*c* 0·66) (Found: C, 72·2; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

Action of Phosphorus Oxychloride in Pyridine on **3α-*Hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide*** (X; R = H).—The hydroxy-compound (0·42 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·5 c.c.) were set aside at room temperature for 24 hr. The solid obtained on dilution with water was collected and recrystallised from ethanol, to give a molecular complex of 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI) and 3-chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide, as plates, m. p. 127—128°, $[\alpha]_D^{17}$ +84·1° (*c* 1·05) (Found: C, 72·1; H, 9·1. $C_{15}H_{22}O_2$,$C_{15}H_{23}O_2Cl$ requires C, 71·7; H, 9·0%). Chromatography on "Woelm" brand acid alumina afforded 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI), m. p. and mixed m. p. 134—135°. The chloro-compound could not be obtained pure.

Reduction of the Ketone (VIII) *with Borohydride.* **3β-*Hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide*** (XI; R = H).—**3-Oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide** (VIII) (1·0 g.) in methanol (20 c.c.) was treated with potassium borohydride (0·70 g.) in water (5 c.c.). After 1 hr., the mixture was acidified, and water (100 c.c.) was added. The product obtained was recrystallised from ethanol, to give **3β-*hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide*** (XI; R = H) (0·78 g.), as needles, m. p. 171—172°, $[\alpha]_D^{18}$ +50·7° (*c* 0·56) (Found: C, 71·5; H, 9·6. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The ***acetate*** (XI; R = Ac), prepared by heating the alcohol with acetic anhydride and pyridine, crystallised from ethanol as needles, m. p. 143°, $[\alpha]_D^{17}$ +63·1° (*c* 1·27) (Found: C, 69·1; H, 9·0. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

3α-*Chloro*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XII).—A mixture of **3β-hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide** (XI; R = H) (1 g.), phosphorus oxychloride (0·5 c.c.), and pyridine was set aside for 24 hr. The mixture was diluted with water and the solid was collected. Crystallisation from ethanol gave **3α-*chloro*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide*** (XII) (1·04 g.), as plates, m. p. 147—148°, $[\alpha]_D^{17}$ −22·2° (*c* 1·02) (Found: C, 66·9; H, 8·6. $C_{15}H_{23}O_2Cl$ requires C, 66·5; H, 8·5%).

Hydrogenation of Sodium Santoninate (XIII) *over Platinum.* **6α-*Hydroxy*-3-*oxo*-4α(H),5β(H)-*eudesman*-13-*oic acid*** (IX).—A solution of sodium santoninate [from santonin (25 g.) and sodium hydroxide (4·0 g.)] in water (300 c.c.) and platinum black (1 g.) were stirred in hydrogen for 60 hr. Acidification of the filtered solution gave **6α-hydroxy-3-oxo-4α(H),5β(H)-eudesman-13-oic acid** (IX; 16 g.), m. p. 190—191° after recrystallisation from aqueous ethanol.

3-*Oxo*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIV).—The above acid (IX) (2·5 g.) was heated at 195° for 30 min. The resulting solid was recrystallised from ethyl acetate–light petroleum, to give **3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide** (1·8 g.), m. p. 100—101°, $[\alpha]_D^{18}$ +10·1° (*c* 0·77). Cusmano[21] records m. p. 105°, $[\alpha]_D$ +9·3°, Yanagita and Tahara,[1] m. p. 96—97°, $[\alpha]_D$ +7·3°, and Kovács *et al.*,[2] m. p. 103—105°, $[\alpha]_D$ +11·3°.

Hydrogenation of the Ketone (XIV) *over Platinum.* **3β-*Hydroxy*-11α(H),4 : 5 : 6β-(H)-*eudesman*-6 : 13-*olide*** (III).—A mixture of **3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide** (XIV) (1·0 g.), platinum oxide (0·1 g.), and acetic acid (20 c.c.) was shaken in hydrogen for 2 hr. The product (III), after crystallisation from ethanol, was obtained as needles (0·75 g.), m. p. and mixed m. p. with an authentic sample 210—211° (see above). The ***acetate*** was obtained as needles, (from ethanol), m. p. 129—130°, $[\alpha]_D^{18}$ +32·7° (*c* 0·46) (Found: C, 69·5; H, 8·6. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

11α(H),5 : 6β(H)-*Eudesm*-3-*en*-6 : 13-*olide* (XV).—A mixture of the preceding compound (III) (1·0 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·3 c.c.) was set aside for 24 hr. at room temperature. The mixture was diluted with water, and the product collected and crystallised from light petroleum followed by aqueous ethanol, giving **11α(H),5 : 6β(H)-*eudesm*-3-*en*-6 : 13-*olide*** (XV) as plates (0·32 g.), m. p. 118—119°, $[\alpha]_D$ −61·2° (*c* 1·2) (Found: C, 76·4; H, 9·2. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

Ozonolysis of **11α(H),5 : 6β(H)-*eudesm*-3-*en*-6 : 13-*olide*** (XV).—The unsaturated compound (0·50 g.) in methyl acetate (50 c.c.) was treated with ozone at −20° for 1 hr., and the ozonide was decomposed by hydrogenation at a palladium–charcoal catalyst. No volatile carbonyl compound was found, but the residual oil gave positive reactions with Tollens's and Schiff's reagents, and also iodoform with sodium hypoiodite.

Reduction of the Ketone (XIV) *with Borohydride.*—(a) *In slight excess.* **3α-*Hydroxy*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide*** (XVI). A solution of **3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide** (XIV) (2·5 g.) in methanol (30 c.c.) was treated with potassium

borohydride (0·14 g.) in water (5 c.c.). After 1 hr. at room temperature the mixture was acidified, and diluted with water, giving a solid product. Crystallisation from ethanol afforded 3α-*hydroxy*-11α(H),4 : 5 : 6β-*eudesman*-6 : 13-*olide* (XVI) as needles (1·9 g.), m. p. 143—144°, $[\alpha]_D$ −38·0° (*c* 0·62) (Found : C, 71·6; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The *acetate* crystallised from ethanol as needles, m. p. 181—182°, $[\alpha]_D^{15}$ −31·9° (*c* 1·06) (Found : C, 68·8; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

(b) *In large excess.* 11α(H),4 : 5β(H)-*Eudesmane*-3 : 6α : 13-*triol* (XVII). 3-Oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (1·0 g.) in methanol (10 c.c.) was treated with potassium borohydride (0·5 g.) in water (10 c.c.). After 24 hr. at room temperature the mixture was acidified and diluted with water, thus affording the *triol* which on recrystallisation from ethanol was obtained as needles (0·54 g.), m. p. 220°, $[\alpha]_D$ −42·6° (*c* 0·77 in MeOH) (Found : C, 70·0; H, 10·8. $C_{15}H_{28}O_3$ requires C, 70·3; H, 11·0%).

3β-*Chloro*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XVIII).—A mixture of 3α-hydroxy-11α(H),4 : 5 : 6β-eudesman-6 : 13-olide (XVI) (0·6 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·3 c.c.) was kept for 24 hr. at room temperature, then poured into water. The product was collected and crystallised from ethyl acetate–light petroleum (60—80°), giving 3β-*chloro*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XVIII) as plates (0·31 g.), m. p. 160°, $[\alpha]_D^{19}$ +30·5° (*c* 0·43) (Found : C, 67·1; H, 8·6. $C_{15}H_{23}O_2Cl$ requires C, 66·5; H, 8·5%).

Reduction of 6α-*Hydroxy*-3-*oxo*-4α(H),5β(H)-*eudesman*-13-*oic Acid* (IX).—(a) *With borohydride.* 3β-*Hydroxy*-4 : 11α(H),5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIX). A solution of the acid (IX) (2·7 g.), potassium hydroxide (0·55 g.), and potassium borohydride (0·25 g.) in aqueous methanol (30 c.c.; 50%) was set aside for 24 hr., then was acidified and heated on a water-bath for 1 hr. Recrystallisation of the product from ethanol gave 3β-*hydroxy*-4 : 11α(H),5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIX) as needles (1·8 g.), m. p. 153—154°, $[\alpha]_D^{14}$ +36·6° (*c* 1·07) (Found : C, 71·0; H, 9·5. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). A second form (rhombs), m. p. 153—154°, was obtained in one experiment. The *acetate* (from ethanol) had m. p. 151—152°, $[\alpha]_D^{17}$ +70·6° (*c* 0·9) (Found : C, 69·5; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

(b) *With platinic oxide.* A mixture of the acid (IX) (1·0 g.), platinic oxide (0·1 g.), and acetic acid (50 c.c.) was stirred in hydrogen for 48 hr., giving 3β-hydroxy-4 : 11α(H),5 : 6β(H)-eudesman-6 : 13-olide (0·60 g.), m. p. and mixed m. p. 153—154°.

Dehydration of 3β-*Hydroxy*-4 : 11α(H),5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIX).—This compound (1·1 g.) on treatment with pyridine (6 c.c.) and phosphorus oxychloride (0·33 c.c.) gave 11α(H),5 : 6β(H)-eudesm-3-en-6 : 13-olide (XV) (0·6 g.), m. p. 117—118°, undepressed by admixture with a sample prepared as above.

2α-*Bromo*-3-*oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XX).—Bromine (1·6 g.) in acetic acid (16 c.c.) was added slowly to 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) (2·5 g.) in acetic acid (12·5 c.c.) containing 30% hydrobromic acid (0·5 c.c.) at 40°. The product, recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), afforded 2α-bromo-3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XX) (2·8 g.) as needles, m. p. 147—148°, $[\alpha]_D^{17}$ +9·4° (*c* 1·33) Yanagita and Tahara [1] record m. p. 145—147°, $[\alpha]_D^{20}$ +8·3° (Found : C, 55·0; H, 6·7. Calc. for $C_{15}H_{21}O_3Br$: C, 54·7; H, 6·4%).

2α-*Chloro*-3-*oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XXI).—2α-Bromo-3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (3·5 g.), lithium chloride (1·5 g.), and dimethylformamide (25 c.c.) were heated at 100° for 2 hr. under nitrogen. The product obtained by dilution with water crystallised from ethanol, to give 2α-*chloro*-3-*oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XXI) as plates, m. p. 178—179° (variable), $[\alpha]_D^{22}$ +19·3° (*c* 0·4) (Found : C, 62·2; H, 7·6. $C_{15}H_{21}O_3Cl$ requires C, 63·2; H, 7·4%).

2β-*Bromo*-3-*oxo*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XXII).—3-Oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV) (2·5 g.) on treatment with bromine (1·6 g.) in acetic acid (15 c.c.) gave 2β-bromo-3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XXII) as needles (3·1 g.) (from ethyl acetate–light petroleum), m. p. 146° [depressed on admixture with (XX)], $[\alpha]_D^{19}$ −7·6° (*c* 1·2) Yanagita and Tahara [1] record m. p. 147—149°, $[\alpha]_D$ −7·55° (Found : C, 54·7; H, 6·6. Calc. for $C_{15}H_{21}O_3Br$: C, 54·7; H, 6·4%).

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875. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part VIII.* The Use of an Infrared Gas Analyser for the Quantitative Determination of Carbon Monoxide.*

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A commercial "Infra-Red Gas Analyser" has been employed to measure the rate of evolution of carbon monoxide arising from the decomposition of pivaloyl chloride by aluminium chloride. The method is more accurate than the titration procedure used earlier,[1] and more flexible, facilitating rapid and consistent measurements on a much wider range of concentrations.

Pivaloyl chloride is decomposed by aluminium chloride to carbon monoxide and *iso*butene, or if an aromatic hydrocarbon is present, a *tert.*-butyl derivative. The rate of this reaction was measured by Rothstein and Saville [1] who titrated the unchanged acid obtained from samples withdrawn from the reaction mixture. The order with respect to the aromatic component was zero and, since the concentration of catalyst remained constant, the reaction afforded a first-order constant of approximately 0·043 min.$^{-1}$ for unit concentration of the aluminium chloride.

The above procedure measures the rate at which carbon monoxide is eliminated only in specially chosen, favourable conditions. The inferences drawn by Rothstein and Saville were valid because it had been ascertained previously that the total yield of gas more or less corresponded with the amount of acid chloride initially taken. In general, expulsion of carbon monoxide may be accompanied by reaction of the acid chloride with any aromatic compound present, or in its absence, with the *iso*butene resulting from the decomposition.[2] In such cases, therefore, estimation of unchanged acid is unsuitable except for measurement of the total reaction. There are also other serious disadvantages inherent in the titration method. The large proportion of reaction which occurs before withdrawal of the first sample limits the concentration of catalyst which can be used. On the other hand, too low a concentration of the acid chloride leads to inaccurate titrations. So it is impossible to investigate the faster reactions or those in which the catalyst is in molecular excess. The procedure is in any case tedious and inflexible and it is by no means certain that the reacting complex yields back all the original acid when it is decomposed. Thus it is not feasible to minimize undesirable side-reactions by the use of relatively high concentrations of catalyst and it is likewise found that the reactions of alkylated acetyl chlorides are unmanageably fast even at low concentrations.

The quantitative estimation of carbon monoxide liberated during a reaction has usually been made volumetrically,[3] but in the present case the nature of the reaction to be studied and the large volume of gas evolved suggested that advantageous use could be made of the 3-box Infra-Red Gas Analyser developed in this country by Messrs. Sir Howard Grubb, Parsons and Co. Ltd. This instrument responds, unless overlapping absorption bands are present, to one particular gas and to no other. The variable sensitivity makes it possible to use gaseous mixtures over a wide range of composition whilst the time of response is usually negligibly small.

Experimental

The Infra-Red Gas Analyser was connected to an "Ether" automatic recorder giving a reading every 30 sec. on a 5" chart graduated horizontally in 100 divisions and vertically at ½" intervals from which the time could be read off. The smallest reading of the horizontal divisions which could be clearly read was approximately 1/200 of the full scale, the exact reading being dependent on the working conditions. Maximum stability was achieved by switching on the Analyser at least 1 hr. before use. Although a voltage stabiliser was fitted, the mains

* Part VII, *J.*, 1952, 4136.

[1] Rothstein and Saville, *J.*, 1949, 1954.
[2] Grundy, Hsü, and Rothstein, *J.*, 1952, 4136.
[3] Schierz, *J. Amer. Chem. Soc.*, 1923, **45**, 447; Dittmar, *J. Phys. Chem.*, 1929, **33**, 533.

frequency variations (about 6%) at peak hours caused serious changes in the sensitivity, necessitating frequent checks by means of the calibrating shutter with consequent corrections to the percentages of carbon monoxide read off the chart. In general, the sensitivity could be adjusted during the preliminary calibration so that a full scale reading of the meter was obtained corresponding to the maximum concentration of carbon monoxide likely to be encountered during a determination. Though a constant-temperature room was not used, the large thermal inertia of the instrument counteracted small variations due to temperature changes.

The speed of response of the Analyser is governed by two factors. One is the electrical nature of the circuit, which causes a delay of 8 sec.; however, readings were recorded every ½ min. and therefore this delay was unimportant. Experimental conditions govern the other. For many experiments an absorption tube 30 cm. long with a capacity of 110 c.c. was used in conjunction with a rate of flow of 200 c.c./minute. It is usually considered that the time taken to replace a gas entirely is that taken for the passage of four times its volume, so that in the above example a complete change was obtained in 2 min. For a steady rate of flow the time lag was constant and significant errors were not introduced. For faster reactions where the higher concentrations of carbon monoxide necessitated a shorter path (*i.e.*, a shorter absorption tube of approx. length 10 cm.) a much shorter response time was obtained.

The Analyser was calibrated by passing artificial mixtures of nitrogen and carbon monoxide through the apparatus until steady readings were obtained. A second method duplicated the subsequent experimental conditions and agreed with the first. A measured flow of carbon monoxide was passed into a stream of nitrogen flowing at a known and constant rate into the Analyser, and the steady readings on the chart were plotted against the known composition of the mixture. This method proved to be rapid and accurate and was therefore extensively employed. The flow of nitrogen was determined by a capillary flowmeter with a capacity of 150—250 c.c./min. For carbon monoxide rates below 1 c.c./min. were measured by a mercury-pellet flowmeter; above this figure and below 100 c.c./min. a soap-bubble flowmeter using soap films made from a mixture of 0·5% aqueous " Aerosol " (3 vols.) and glycerol (1 vol.) was found to be convenient.

Nitrogen at constant pressure from a cylinder was passed through a capillary-type flowmeter and washed by concentrated sulphuric acid and then activated alumina. From there the gas passed into four wash-bottles, three of which were immersed in the thermostat. These contained benzene in order to saturate the nitrogen with vapour and to adjust its temperature to that of the reaction mixture. After passing through a condenser, the mixed gases were washed with water and dried by concentrated sulphuric acid which also removed any olefin formed during the reaction, and finally passed through a small tube containing anhydrous calcium chloride and a small cotton wool filter into the Analyser. The bulb of a thermometer was inserted into the stream of issuing gases which were insulated from external heat effects. Before the commencement of an experiment, *i.e.*, before addition of the acid chloride, nitrogen was swept through the apparatus and the zero adjusted to compensate for the small deflection due to benzene (calibration having been carried out under these conditions). The time for the maximum deflection during a reaction was dependent on the rate of flow of nitrogen and on the length of absorption tube used. It varied from 6 to 30 min. and accordingly the exact commencement of the reaction could not be determined from the graph. No serious error was introduced, however, by assuming that the reaction started 30 sec. before the first positive reading on the recorder.

Preparation of Materials and Method of Reaction.—Aluminium chloride was prepared in an electric furnace from aluminium turnings and hydrogen chloride.[4] The product was resublimed in a current of dry hydrogen chloride, then in a stream of dry nitrogen, and finally stored over phosphoric oxide in aluminium-capped bottles. It was a fine, nearly white powder, easily soluble in nitrobenzene. The benzene was sulphur-free and of molecular-weight quality. It was dried (Na) and redistilled. The nitrobenzene (" AnalaR ") was likewise dried ($CaCl_2$) and redistilled. Solutions of the freshly distilled acid chloride in benzene, and of aluminium chloride in nitrobenzene, were prepared in graduated flasks and brought to the temperature of the thermostat. The concentration of nitrobenzene (by volume) was maintained throughout the experiments at 20 c.c. in 180 c.c. of reacting solution.

The required quantity of benzene was added from a burette to a three-necked reaction flask immersed in the thermostat. The flask was fitted with a mercury-seal stirrer, an inlet tube, and a double-surface condenser to which was attached a guard-tube containing calcium

[4] Dawson, *J. Amer. Chem. Soc.*, 1928, **50**, 133.

chloride. The solution of aluminium chloride was then added, followed by that of the acid chloride. The gaseous products of the reaction were swept out by nitrogen (flowing at about 200 c.c./min.), the liquid being rapidly and continuously stirred in order to obtain a smooth trace on the recorder.

Calculation of Results.—The recorder furnished a curve showing variation of scale-reading against time. This was converted by means of the sensitivity calibration curve into a graph showing the percentage of liberated carbon monoxide at any time (t) and integration afforded a figure of the actual volumes of the gas evolved in a selected interval of time.

Absolute constancy in the flow of nitrogen was not attainable and the slight variations during each 30 min. period, the interval adopted for the calculation in the slower reactions, were averaged. The volume V c.c. of carbon monoxide evolved per minute was given by :

$$V = \frac{273}{T} \times \frac{P}{760} \times 60 \times F \times \frac{0{\cdot}05 \times 0{\cdot}3 \times N}{100}$$

where T is the absolute temperature of the mixed gases, P is their pressure (mm. Hg), F (c.c./sec.) is the rate of flow of nitrogen, and N the number of integration squares in the appropriate units; this volume was subject to a correction dependent on the purity (usually ~97·9%) of the carbon monoxide used in calibrating the gas analyser.

Results.—In Table 1 are given details of three experiments to illustrate consistency. The decrease in the first-order constant may be attributed partly to ketone formation as a result of reaction between the acid chloride and the product, *tert.*-butylbenzene (cf. Part VII [9]), and partly to the decrease in the efficiency of the catalyst owing to complex formation between it and the ketone. The first-order constant for the particular concentration of aluminium chloride

TABLE 1.

$AlCl_3$ = 0·063 mole/l. $CMe_2{\cdot}COCl$ = 0·326 mole/l. Temp., 20·36°.

	CO (mole/l.) (corr.)			10^2k_1 (min.$^{-1}$)		
Time (min.)	Expt. 1	2	3	Exp. 1	2	3
60	0·050	0·049	0·052	0·273	0·271	0·288
120	0·084	0·088	0·092	0·250	0·259	0·275
180	0·109	0·116	0·121	0·229	0·243	0·258
240	0·128	0·136	0·143	0·208	0·225	0·241
300	0·143	0·151	0·159	0·192	0·208	0·222
360	0·154	0·163	0·170	0·178	0·193	0·206
	10^2k_1 (extrapolated)			0·295	0·292	0·308

was obtained by extrapolation of the individual constants back to zero time in the case where acid chloride was greatly in excess of aluminium chloride. In all other cases, the figure over the time indicated was calculated by the method of least squares (although usually the figures obtained by the two methods were nearly identical); in these cases there was not a continuous variation in the value of k_1 (cf. Table 2).

More consistent figures for the first-order constant were obtained when the catalyst was in excess. Table 2 shows reasonably constant figures up to 85% of the reaction (120 min.).

TABLE 2.

$[AlCl_3]$ = 0·15 mole/l. $[CMe_2{\cdot}COCl]$ = 0·05 mole/l. Temp., 20·36°.

Experiment 31.

Time (min.)	30	60	90	120	150	180	210	240
CO (mole/l.) (corr.)	0·0198	0·0316	0·0385	0·0427	0·0451	0·0470	0·0481	0·0490
10^2k_1 (min.$^{-1}$)	1·68	1·67	1·63	1·60	1·55	1·56	1·52	1·63

10^2k_1 = 1·74 min.$^{-1}$ (extrap.), 1·65 min.$^{-1}$ (not extrap.; 60 min.).

A direct comparison with the titration method was carried out by arranging duplicate reactions in the same thermostat. In the titration method it is possible to calculate the first-order constant from the slope of the curve obtained by plotting log concentration against time, because, owing to compensatory influences, side-reactions have a smaller effect on the consumption of the acid chloride. The two determinations, in which the concentrations and temperature of Table 1 were used, afforded a mean value for 10^2k_1 of 0·299 min.$^{-1}$, negligibly different from that of 0·298 min.$^{-1}$ derived from the previous measurements. Slight differences in the first-order constants determined by the two methods barely reflect real differences since the rapid *initial* consumption of acid chloride is not paralleled by a very rapid rate of elimination of carbon

monoxide. Although there is some uncertainty about the exact zero time, a comparison of acid chloride concentrations estimated by the two procedures (Table 3) shows a lag in the evolution of carbon monoxide which is apparently partly due to irreversible formation of a complex which has a finite time of decomposition, and partly due to side-reactions mentioned above.

TABLE 3. *Pivaloyl chloride remaining after time, t. Concns. and temp. as in Table* 1.

t (min.)	60	120	180	240	300	360
Titration method (%)	74·2	60·1	49·7	42·3	36·5	31·9
CO evolution method (%)	84·6	72·9	64·6	58·4	52·5	49·3
Difference (%)	10·4	12·8	14·9	16·1	16·0	17·4

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876. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part IX.* Concentration and Environmental Factors influencing the Elimination of Carbon Monoxide from Pivaloyl Chloride.*

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The rate of elimination of carbon monoxide from pivaloyl chloride, catalysed by aluminium chloride is of the first order with respect to the concentration of the acid chloride and of the second in the concentration of catalyst. Unlike in ketone synthesis, the rate constant is unaffected by the ratio of aluminium chloride to acid chloride. Preliminary experiments show a 60—100% increase in the rate of reaction for a temperature rise of 2°, and an increase in the dielectric constant of the solvent also accelerates reaction. Although the rate of elimination of carbon monoxide is independent of the aromatic component, experiments in toluene demonstrate that this is not the case for ketone formation. It appears, from the examination of the two reactions in competition, that the probable rate-determining stage for elimination of carbon monoxide is the formation of the reactive complex from aluminium chloride and the acid derivative. Substitution of pivalic anhydride for pivaloyl chloride affords substantially unchanged reaction rates but some deactivation is apparent.

The kinetic results are discussed in relation to those obtained for Friedel–Crafts alkylations and acetylations by previous investigators. It is shown that the postulate of a preliminary equilibrium involving the catalyst, similar to that proposed by N. N. Lebedev, is justified, but structures for the catalyst and the catalyst–halide complex put forward by this author are rejected. In particular, deactivation, not activation, results from co-ordination of aluminium chloride by the oxygen atom of the acid halide.

DECOMPOSITION of pivaloyl chloride by aluminium chloride appears to be a first-order reaction with respect to the acid chloride although side-reactions lead to small variations in the value of the first-order constant.[1] Ketonic products which reduce the activity of the catalyst can in some cases be isolated.[2] Their formation depends on the composition of the solvent, the concentration of the acid chloride, and on the conditions.[3] Even in optimum conditions the *tert.*-butylbenzene obtained by the condensation of pivaloyl chloride and benzene exhibits a strong carbonyl absorption peak in the infrared spectrum. Though the presence of the ketone could not be detected by ordinary analytical methods, the possibility of its formation was inferred because the yields of carbon monoxide actually isolated were never greater than 80—90%.

Rothstein and Saville found [1] that for a particular concentration of catalyst the first-order constant was independent of the ratio of pivaloyl chloride to aluminium chloride

* Part VIII, preceding paper.

[1] Rothstein and Saville, *J.*, 1949, 1954.
[2] Pearson, *J. Amer. Chem. Soc.*, 1950, **72**, 4169.
[3] Grundy, Hsü, and Rothstein, *J.*, 1952, 4136.

concentrations over the range 5—10 : 1. Except for very high ratios (Table 1, expts. 1, 2, 3, 4, and 88), the carbon monoxide method also shows that the rate constant is independent of both the initial concentration of the pivaloyl chloride and its concentration relative to that of the aluminium chloride.

It had been noted by Rothstein and Saville [1] that aluminium chloride entered the rate equation approximately as the square of its concentration. This was correspondingly the case for the elimination of carbon monoxide. The rate constants for a number of different concentrations of aluminium chloride (see Table 2) satisfy the equation (calculation 1), $k_1^{20\cdot36} = 0{\cdot}5879[AlCl_3]^2 + 0{\cdot}000847$, but a much more accurate expression, particularly for smaller concentrations of catalyst (calculation 2) is: $k_1^{20\cdot36} = 0{\cdot}4928[AlCl_3]^2 + 0{\cdot}025[AlCl_3] - 0{\cdot}00037$. The justification for including a term involving the first power of catalyst concentration is discussed later. The reaction orders calculated from $n = (\log k - \log k')/(\log [AlCl_3] - \log [AlCl_3]')$ vary slightly from 1·80 for the lowest to 1·90 for most experiments.

TABLE 1. *Effect of variation in acid chloride concentration.*

Temp. for "A" = 20·36°; for "B" > 20·36°. "Carbon monoxide" method.

	"A"			"B"			
Expt. no.	(1, 2, 3, 4)	(8, 9)	11	88	87	86	85
$[CMe_3{\cdot}COCl]$ (mole/l.)	0·326	0·163	0·082	0·100	0·075	0·050	0·025
$[AlCl_3]$ (mole/l.)	0·063	0·063	0·063	0·050	0·050	0·050	0·050
10^3k_1 (min.$^{-1}$)	0·298	0·301	0·305	0·223	0·261	0·257	0·261

TABLE 2. *Effect of variation in catalyst concentration.*

Temp., 20·36°. "Carbon monoxide" method.

		10^3k_1 (min.$^{-1}$)					10^3k_1 (min.$^{-1}$)		
Expt. no.	$[AlCl_3]$ (mole/l.)	Found	Calc. (1)	Calc. (2)	Expt. no.	$[AlCl_3]$ (mole/l.)	Found	Calc. (1)	Calc. (2)
10	0·01575	0·029	0·099	0·011	24, 25, 26, 27	0·100	0·698	0·673	0·706
5, 6	0·0315	0·106	0·143	0·091	37	0·125	0·923	1·000	1·049
20, 21, 22	0·050	0·223	0·232	0·211	29, 30, 31	0·150	1·468	1·408	1·447
1, 2, 3, 4	0·063	0·298	0·318	0·317	32, 33	0·200	2·434	2·437	2·434
38	0·833	0·515	0·493	0·513	34, 35, 36	0·250	3·668	3·760	3·651

The existence of a rather steep temperature gradient for the reaction was confirmed by repeating some of the determinations at the standard temperature (20·36°) ± 2° (see Table 3). The higher temperatures were, in each case, associated with decreased side-reactions.

TABLE 3. *Effect of temperature on elimination of carbon monoxide.*

$[CMe_3{\cdot}COCl]$ (mole/l.)	0·326			0·326		0·025	
$[AlCl_3]$ (mole/l.)	0·0315			0·063		0·125	
Expt. no.	12	5	13, 16, 17	1—4	14, 15	37	18, 19
Temp.	19·36°	20·36°	22·36°	20·36°	22·36°	20·36°	22·36°
10^3k_1 (min.$^{-1}$)	0·095	0·110	0·179	0·298	0·507	0·923	2·01

TABLE 4. *Reaction constants in benzene and carbon tetrachloride.*

$[CMe_3{\cdot}COCl] = 0{\cdot}326$ mole/l. $[AlCl_3] = 0{\cdot}063$ mole/l.

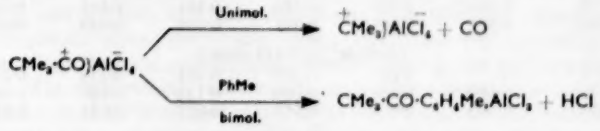
			Time (min.)							Reaction
Expt. no.	Solvent		30	60	90	120	150	180	210	(%)
1	C_6H_6–$Ph{\cdot}NO_2$	10^3k_1 =	—	0·27	—	0·25	0·23	0·23	—	39
46	CCl_4	10^3k_1 =	0·16	0·16	0·16	0·16	0·16	0·16	0·155	25
47	"	10^3k_1 =	0·17	0·17	0·17	0·17	0·16	0·16	0·16	28

The possibility was next explored of using solvents other than the benzene–nitrobenzene mixture which had been employed hitherto, but it was found that the reactions in nitromethane or in *s.*-tetrachloroethane were slow and unreliable. Carbon tetrachloride afforded consistent results, and the curve obtained showed a complete absence of side-reactions (Table 4). The limited solubility of aluminium chloride, however, prevented a more

extensive use of this solvent. The slow reaction rate is typical of that commonly noticed when non-polar solvents are used and will be referred to below.

The contrary was true of reactions in nitrobenzene. The initial vigorous evolution of gas was too great to be measured and ceased after a few minutes. The titration method showed that over 50% of the acid chloride had disappeared in the first few minutes and about 70% (0·22 mol.) in a little more than an hour. Cessation of the reaction resulted from the deactivation of the catalyst, and addition of a further quantity of a nitrobenzene solution of aluminium chloride restarted the decomposition. It is clear that the complex said to be formed from the catalyst and nitrobenzene can still accelerate the reaction. There was no accelerating effect when more of the acid chloride was added.

The next experiments were designed to compare the decomposition with ketone formation. Rothstein and Saville [4,5] observed that pivaloyl chloride and toluene afford a mixture of *tert.*-butyl *p*-tolyl ketone and *p-tert.*-butyltoluene and it was postulated that whereas the first of these results from a first-order reaction with regard to toluene, the second arises from a reaction which is of zero order in this respect :



Thus by performing the reaction in carbon disulphide, with increasing concentrations of toluene, the ratio hydrocarbon : ketone should diminish, as is the case (Table 5).

TABLE 5. *Reaction between pivaloyl chloride and toluene, with various concentrations of toluene in carbon disulphide.*

Acid titration method. $[CMe_3{\cdot}COCl] = 0{\cdot}50$ mole/l. $[AlCl_3] = 1{\cdot}5$ mole/l.

[PhMe] (mole/l.)	Yield of ketone (%)	Yield of hydrocarbon (%)	Ratio, Hydrocarbon : ketone
1	10	50	5 : 1
2	16	47	3 : 1
5	21	42·6	2 : 1

Owing to the nature of the solvent these experiments could not be adapted without modification for quantitative study by the carbon monoxide method. Accordingly, carbon disulphide was replaced by benzene, and toluene by anisole which when in excess is known [4] to yield almost exclusively *tert.*-butyl *p*-methoxyphenyl ketone. In dilute benzene solution *p-tert.*-butylanisole is no doubt also produced although this has not been isolated from the reaction mixture (see below). The different results obtained in the two methods of estimation can be discussed only qualitatively, because the conditions could not be made identical for both sets of experiments.

Inspection of Table 6 suggests that any ketone formation occurs mainly at the commencement of the reaction, since the extrapolated reaction constants decrease with increase in anisole concentration. It is also apparent that not all the differences are due to acylation; were this the case the reaction would cease in the initial stages owing to deactivation of the catalyst. The reaction with an anisole concentration of 0·063 mole/l. was repeated with a view to the isolation of the ketone : the yield of the latter was 0·045 mole/l., *i.e.*, considerably less than that indicated in Table 6. Even so, the catalyst is not deactivated to anything like the extent that would be expected were two-thirds of it combined with the ketone (compare expts. 5, 6, 7). It appears likely that ketone–catalyst combination is not instantaneous and that the titration method suffers from the defect that not all the acid is recoverable from the acid chloride–catalyst complex—no doubt a portion of this complex decomposes before the reaction can be completely quenched. Experiment " B " confirms the first conclusion. No carbon monoxide is eliminated, ketone being the

[4] Rothstein and Saville, *J.*, 1949, 1950.
[5] *Idem*, *J.*, 1949, 1959.

sole product. Yet the yield is more than twice as great as would be expected if catalyst deactivation ran parallel to formation of the product. Olivier [6] likewise noticed that the addition of benzophenone to a reacting mixture of the benzoyl chloride–aluminium chloride complex and benzene failed to reduce the reaction velocity. On the other hand, addition of benzophenone to the above complex in crystalline condition led to the formation of a liquid which slowly deposited crystalline benzophenone–aluminium chloride. The mixture was then completely inert to benzene.

TABLE 6. *Effect of added anisole on the reactions of pivaloyl chloride in benzene.* I, Loss of CO (mole/l.) at 20·36°. II, Loss of CMe_3·COCl (mole/l.) at 20·00°. [CMe_3·COCl] = 0·326 mole/l. [$AlCl_3$] = 0·063 mole/l.

Expt. no.		Time (min.) 0	60	120	180	240	300	10^2k_1 (min.$^{-1}$)
				[Anisole] = 0 mole/l.				
5, 6, 7	I †	0	0·018	0·031	0·049	0·061	0·071	0·106
1, 2, 3, 4	I	0	0·050	0·088	0·115	0·136	0·151	0·298
H1, H2	II	0·034 *	0·091	0·129	0·161	0·185	0·202	—
	Diff.	0·034	0·041	0·041	0·046	0·049	0·051	—
				[Anisole] = 0·015 mole/l.				
39, 40	I	0	0·047	0·077	0·101	0·118	0·129	0·280
A1, A2	II	0·009 *	0·054	0·090	0·118	0·139	0·160	—
	Diff.	0·009	0·007	0·013	0·017	0·021	0·031	—
				[Anisole] = 0·0315 mole/l.				
43	I	0	0·030	0·048	0·061	0·071	0·078	0·190
B	II	0·144 *	0·168	0·181	0·191	0·200	0·207	—
	Diff.	0·142	0·138	0·136	0·135	0·136	0·137	—
				[Anisole] = 0·063 mole/l.				
41	I	0	0·024	0·040	0·050	0·057	0·062	0·168
C	II	0·142 *	0·162	0·176	0·185	0·193	0·199	—
	Diff.	0·142	0·138	0·136	0·135	0·136	0·137	—
				[Anisole] = 0·126 mole/l.				
42	I	0	0·016	0·023	0·027	0·029	—	0·101
D	II	0·008 *	0·043	0·059	0·074	0·081	—	—
	Diff.	0·008	0·027	0·036	0·047	0·052	—	—
				[Anisole] = solvent				
" B " [19]	II	0·074 *	0·098	0·110	0·120	0·128	0·133	—

* Approx. 3 min. after mixing. † [$AlCl_3$] = 0·0315 mole/l.

The Reaction with Pivalic Anhydride.—The Friedel–Crafts reaction with acid anhydrides is usually carried out by using rather more than two mols. of catalyst for each mol. of anhydride, partly because of the deactivation of the catalyst by the ketone produced and partly because one of the products is the dichloroaluminium salt of the acid :

$$(R{\cdot}CO)_2O + 2AlCl_3 + ArH \longrightarrow RArCO,AlCl_3 + HCl + R{\cdot}CO{\cdot}O{\cdot}AlCl_2$$

It has been stated that the acetic acid resulting from the preparation of *p*-chloro- and *p*-bromo-acetophenone from the halogenobenzenes and acetic anhydride is itself capable of affording more of the acetophenone.[7] Even at the relatively high temperature of the reaction (100°) the quoted yields are 97% and 99% based on the anhydride. Acetyl chloride can indeed be prepared from the acid and aluminium chloride, but not under the conditions described in *Org. Synth.*[8] In the experiments to be described, the yield was not greater than 98% based on the equation :

$$(CMe_3{\cdot}CO)_2O + C_6H_6 \xrightarrow{AlCl_3} CMe_3Ph + CO + CMe_3{\cdot}CO_2H$$

even when the catalyst was employed in 5 : 1 excess. The results of present experiments cast doubt on the catalytic inactivity of the dichloroaluminium salt. Table 7 shows some

[6] Olivier, *Rec. Trav. chim.*, 1918, **37**, 205.
[7] *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 111.
[8] Groggins, Nagel, and Stirton, *Ind. Eng. Chem.*, 1934, **26**, 1317.

deactivation with the lower concentration of catalyst (expt. 44) but hardly any at the higher concentration (expt. 45) compared with the corresponding reactions with pivaloyl chloride (k_1 = 0·923 and 3·67 min.$^{-1}$ respectively, see Table 3). The values of k_1 are considerably

TABLE 7. *Reactions between pivalic anhydride and benzene.*

Expt. no.	$[(CMe_3 \cdot CO)_2O]$ (mole/l.)	$[AlCl_3]$ (mole/l.)	Method of Estimation	Temp.	10^3k_1 (min.$^{-1}$)	Total reaction (%)
—	0·0473	0·125	Titration	20·00°	0·530	87
44	0·05	0·125	Co detn.	20·36	0·700	76
45	0·05	0·250	Co ,,	20·36	3·48	98

higher than would be expected if deactivation of the catalyst resulted from the formation dichloroaluminium salts, *i.e.*, the effective concentration of catalyst in expts. 44 and 45 would be decreased to 0·075 and 0·200 mole/l., affording calculated values of 10^2k_1 of 0·428 and 2·43 respectively, instead of those actually obtained. There was, however, a strictly linear relation between log [acid anhydride] and time for at least 50% of the reaction and a marked acceleration towards the end. The final readings for the first experiment were made at 361 min. and 500 min. and these were found to be identical; therefore the reaction had reached completion before the former time. Thus there was no indication, in spite of the final acceleration, that the pivalic acid liberated during the reaction itself underwent decomposition. The very smooth reaction is in accordance with the usual observation that acid anhydrides are preferable to acid chlorides in the Friedel–Crafts reaction. As regards the final acceleration it is of course possible that hydrogen chloride liberated during the reaction regenerated the catalyst.

DISCUSSION

Elimination of carbon monoxide is related to acylation, but because the concentration of the catalyst remains substantially constant, kinetically it resembles Friedel–Crafts alkylations and allied syntheses. Both acylation and alkylation are characterised by a variable order with respect to the catalyst, depending on the nature of the latter and the solvent employed. Examples of reactions dependent on the square of the catalyst concentration are the aluminium chloride-catalysed interconversion of *m*- and *p*-cresol,[9] and the methylation and ethylation of benzene with gallium trichloride.[10] On the other hand, the corresponding order for aluminium chloride in the formation of benzophenone is less than unity, that for the alkylation of benzene by 3 : 4-dichlorobenzyl chloride in nitrobenzene solution is unity. The rate-controlling step of the second reaction was shown by H. C. Brown and Grayson to be the interaction of the alkyl chloride–catalyst complex with benzene,[11] and this it will be shown should lead to first-order dependence on the catalyst concentration, as actually observed. A mechanism which elucidates the kinetics associated with the elimination of carbon monoxide, should, with the necessary changes, be equally applicable to both alkylation and acylation, and the following considerations support this view. It is reasonable to assume that the addition product of pivaloyl chloride with aluminium chloride has the same structure as that formed from other acyl halides and is therefore a 1 : 1 compound (cf. Olivier,[6] and below). This is because ketones can in fact be obtained from pivaloyl chloride. It is not implied that, because the slow step in ketone formation is the actual acylation of benzene, the correspondingly slow step in the decomposition reaction is the elimination of carbon monoxide, for there would be an accumulation of intermediate which would afford ketone even with the comparatively unreactive benzene. The diminished rate of the decomposition in the presence of quite small quantities of anisole (Table 6) is evidence that the rate-determining stage is that of complex formation. It is true that any ketone formed will eventually deactivate the catalyst but it has previously been indicated that this is a relatively slow reaction and would not be very effective initially, so that the reduced rate constants obtained by extrapolation to zero time are confirmation that a competitive reaction follows a slow one.

[9] Baddeley, *J.*, 1943, 527.
[10] H. C. Brown, Jungh, and Smoot, Symposium on the Friedel–Crafts Reaction, Leeds, 1955.
[11] H. C. Brown and Grayson, *J. Amer. Chem. Soc.*, 1953, **75**, 6285.

Although it has recently been disputed by Korshak and N. N. Lebedev,[12, 13] it is usually considered that the acylation of the benzene nucleus is by an acyl cation $R{\cdot}CO^+$. An independent cation is not necessarily involved, and the reacting entity is more probably the ion pair $R{\cdot}CO^+\}AlCl_4^-$, as in essentials was originally suggested by Boeseken,[14] by Olivier,[6] and, in 1927, more explicitly by Meerwein.[15] Olivier concluded that the rate-determining step was the bimolecular reaction between the complex ($R{\cdot}COCl,AlCl_3$) and benzene. All these authors appear to have assumed the simple addition of acid halide to monomeric catalyst. In analogy with the acid chloride it seems reasonable to formulate the acid anhydride–catalyst complex as $(R{\cdot}CO)_2O^+,AlCl_3^-$ though this does not exclude other structures such as $(R{\cdot}CO)^+(R{\cdot}CO{\cdot}O,AlCl_3)^-$ which are in resonance with the first one.

Korshak and Lebedev remark on the tendency to ignore the dimeric nature of the catalyst and suggest that there is a preliminary equilibrium involving the catalyst and the solvent. A hypothesis of the kind would also account for the kinetic results described in this paper. The above authors consider that the catalyst (unsolvated) reacts as a dipolar ion, the dipole moment not being observable because of the resonance between structures such as $Cl_2Al^+ \cdots AlCl_4^-$ and $Cl_4Al^- \cdots AlCl_2^+$. It must be said however, that derived structures such as $(R{\cdot}COCl)Al_2Cl_6$ and $(R{\cdot}CO^+ \cdots AlCl_3)\ AlCl_4^-$ have in fact been proposed by various authors,[16] and it is not the case that aluminium halides always have the dimeric form known to occur in the solid or the gaseous state. Dimerisation depends both on solvent and concentration, the monomeric form existing as solvated molecules in solvents of high dielectric constant. Association of aluminium bromide, for instance, is nearly complete in benzene or carbon disulphide [6] but only slightly so in nitrobenzene. The 1 : 1 complexes of nitrobenzene with aluminium chloride and bromide are only partially associated in benzene, not more than 10% in dilute solution.[17] Similarly the dipole moment of aluminium bromide in carbon disulphide [18] at infinite dilution is zero, in benzene is $\sim 5 + 10^{-18}$, and in a mixture of benzene and nitrobenzene (one equivalent) is $\sim 9{\cdot}3 + 10^{-18}$ e.s.u. Lebedev [13] maintains that a dimeric form of the reacting complex is the acylating agent, but cryoscopic measurements again indicate that association varies with concentration, being 14% for 0·1M-solution and 87% for 0·3M-solution. Olivier [6] noted a 30% rise in the rate constant when the concentration was doubled (66% association), but this increase was negligible compared with that occurring when excess of catalyst was present. It seems probable that only the monomeric aluminium halide forms complexes with the solvent since the dipole moment of the dimeride is zero, *i.e.*, there is the equilibrium :

$$2(AlCl_3)^-,Ph{\cdot}NO_2^+ \rightleftharpoons Al_2Cl_6 + 2Ph{\cdot}NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

Lebedev [19] formulates an initial equilibrium somewhat differently and considers that only the fully ionised complex functions as the catalyst through its positive ion :

$$[(C_6H_5{\cdot}NO_2)_2^+,AlCl_2^-]^+ + AlCl_4^- \rightleftharpoons [(C_6H_5{\cdot}NO_2)_2^+,AlCl_2^-]^+[AlCl_4]^-$$

which, when solvation is neglected, is equivalent to :

$$AlCl_2^+ + AlCl_4^- \rightleftharpoons AlCl_2^+AlCl_4^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

Since the undissociated complex is in the form of a dipolar ion and the reacting portion of the molecule is the solvated aluminium dichloride it does not appear that there should be much difference in the reactivity between the un-ionised and the ionised compound. Kinetically, reactions (i) and (ii) are equivalent but the advantage of the latter is that it proposes a structure equivalent to that also suggested by Lebedev for the reacting complex

[12] Korshak and N. N. Lebedev, *Zhur. obshchei Khim.*, 1950, **20**, 266.
[13] N. N. Lebedev, *ibid.*, 1951, **21**, 1788.
[14] Boeseken, *Rec. Trav. chim.*, 1900, **19**, 19; 1901, **20**, 102.
[15] Meerwein, *Annalen*, 1927, **455**, 227.
[16] Perrier, *Compt. rend.*, 1893, **116**, 1296; *Ber.*, 1900, **33**, 815; Dilthey, *Ber.*, 1938, **71**, 1350.
[17] Ulich, *Z. phys. Chem.*, 1931, *Bodenstein Festband*, p. 423.
[18] Nespital, *ibid.*, 1932, *B*, **16**, 176.
[19] Lebedev, *Zhur. obshchei Khim.*, 1954, **24**, 664.

prepared from acid or alkyl chlorides. In general, both the monomeric and the dimeric aluminium halides can be expected to function as catalysts, though not necessarily with equal efficiency. Except in particular experiments, the composition of the solvent in the present work was kept constant; the concentration of nitrobenzene was greatly in excess of that required for 1 : 1 complex formation and consequently it can be omitted from the following considerations, *i.e.*, there are no changes in equilibrium constants due to changes in solvent composition. Since a termolecular reaction is unlikely it is usually assumed that the reaction takes place in stages, of which the second or third may be slow :

$$2AlCl_3 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Al_2Cl_6 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$AlCl_3 + R{\cdot}COCl \underset{k_4}{\overset{k_3}{\rightleftharpoons}} (R{\cdot}CO^+\ AlCl_4^-) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$Al_2Cl_6 + R{\cdot}COCl \underset{k_4'}{\overset{k_3'}{\rightleftharpoons}} (R{\cdot}CO^+\ AlCl_4^-) + AlCl_3 \quad . \quad . \quad (2a)$$

$$(R{\cdot}CO^+\ AlCl_4^-) \xrightarrow{k_5} \text{Products} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Alternatively :

$$Al_2Cl_6 + R{\cdot}COCl \underset{k_4''}{\overset{k_3''}{\rightleftharpoons}} (R{\cdot}CO^+\ Al_2Cl_7^-) \quad . \quad . \quad . \quad . \quad (2b)$$

$$(R{\cdot}CO^+\ Al_2Cl_7^-) \xrightarrow{k_5'} \text{Products} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

Stationary states involving the complex and the catalysts lead to the expression :

$$[R{\cdot}CO^+\ AlCl_4^-] = \frac{k_3[AlCl_3][R{\cdot}COCl]}{k_4 + k_5} + \frac{k_1k_3'[AlCl_3]^2[R{\cdot}COCl]}{\{k_3'[R{\cdot}COCl] + k_2\}\{k_4'[AlCl_3] + k_5\}}$$

Whence $d[CO]/dt = k_5[R{\cdot}CO^+\ AlCl_4^-]$

$$= \frac{k_3k_5[AlCl_3][R{\cdot}COCl]}{k_4 + k_5} + \frac{k_1k_3'k_5[AlCl_3]^2[R{\cdot}COCl]}{\{k_3'[R{\cdot}COCl] + k_2\}\{k_4'[AlCl_3] + k_5\}}$$

If (2) and (2*a*) are the rate-determining steps, *i.e.*, $k_5 \gg k_4$ or $k_4'[AlCl_3]$, and $k_2 \gg k_3'[R{\cdot}COCl]$, then

$$d[CO]/dt = k_3[AlCl_3][R{\cdot}COCl] + Kk_3'[AlCl_3]^2[R{\cdot}COCl] \quad . \quad . \quad . \quad (4)$$

Thus the constant k, for the integrated equation, is given by $k = \{k_3[AlCl_3] + Kk_3'[AlCl_3]^2\}$, corresponding to the experimental results.

If, in the corresponding alkylation reactions (where R·CO is replaced by R), equation (3) represents the slow reaction,[18] *i.e.*, k_4 and $k_4'[AlCl_3]$ are both very much greater than k_5, then the reaction becomes of the first order in the catalyst since

$$\text{rate} = \frac{k_3k_5}{k_4}[AlCl_3][R{\cdot}COCl] + \frac{k_1k_3'k_5}{k_2k_4'}[AlCl_3][R{\cdot}COCl]$$

$$= k_5[R{\cdot}COCl][AlCl_3](K' + KK''), \text{ where } K = k_1/k_2,\ K' = k_3/k_4, \text{ and } K'' = k_3'/k_4'.$$

However, in applying the foregoing equations to alkylations, cognizance must be taken of the basic strength of the halide, deactivation of the catalyst, and other factors. There seems to be no instance where the reaction is other than of the first order with respect to the halide and to the aromatic component in so far as they enter into the rate equations.

The alternative equations (2*b*) and (3*a*) assume dimeric aluminium chloride to be

included in the reactive intermediate, and the rate of reaction then depends on the square of the catalyst concentration even though (3*a*) is rate-determining, since

$$\frac{d[CO]}{dt} = \frac{k_3k_5[AlCl_3][R{\cdot}COCl]}{(k_4 + k_5)} + \frac{k_1k_3''k_5'[AlCl_3]^2[R{\cdot}COCl]}{\{k_3''[R{\cdot}COCl] + k_2\}(k_4'' + k_5')}$$

$$= K'k_5'[AlCl_3][R{\cdot}COCl] + KK'''k_5'[AlCl]^2[R{\cdot}COCl]$$

where $K''' = k_3''/k''$, $k_4 \gg k_5$, $k_4'' \gg k_5'$, and $k_2 \gg k_3''[R{\cdot}COCl]$.

The experimental data suggest that the equilibrium constant K is small even in a solvent containing no more than 10% of nitrobenzene, and further that monomeric solvated aluminium chloride is relatively inefficient as a catalyst. The acceleration associated with increased concentrations of nitrobenzene could be partially attributed to increasing polar effects on the various equilibria, particularly those involving the monomeric and dimeric catalysts with the acid halide. A detailed study of the influence of solvent variation on reaction velocity has not yet been made for pivaloyl chloride, but alkylation of benzene by *cyclo*hexyl chloride in different mixtures of benzene and nitrobenzene has been investigated by Lebedev [19] who recorded a decrease in the reaction order as regards aluminium chloride as the proportion of nitrobenzene in the solution increased. In 85% nitrobenzene the order was 0·4; it was 1·4 in 23% solution, the extrapolated value for pure benzene being 2. Brown and Grayson [11] on the other hand observed an order of one in nearly pure nitrobenzene for alkylation by 3 : 3-dichlorobenzyl chloride. Lebedev's explanation, based on the increasing dissociation of the aluminium chloride–nitrobenzene complex and the greater catalytic activity of the dissociated than of the undissociated compound (equation ii), is unsatisfactory since these assumptions cannot explain orders ranging between the two extreme values and moreover do not envisage the effect of increasing dielectric constant on the reaction in general. He suggests that the dependence on the square root of the catalyst concentration arises from the only slightly dissociated complex, presuming that the dissociated cation is the more effective catalytically, but in that case the postulated very slow reaction catalysed by the ***undissociated*** complex cannot have an order greater than one. The alternative (not suggested by Lebedev) that the undissociated catalyst is the more effective and that it is largely dissociated in nitrobenzene–benzene solution provides an explanation for a two-fold, but not for a fractional, order. This second scheme is in better accord with the physical evidence, but since there is no kinetic work other than Lebedev's which deals with this point, a final decision cannot be made.

The structures of the reactive intermediates as usually formulated, namely $R{\cdot}CO^+\ AlCl_4^-$ and $R^+\ AlCl_4^-$, are not accepted by Lebedev who instead suggests a dimeric formula, $\{(RR'C{:}O)_2AlCl_2\}^+AlCl_4^-$ (RR′ = alkyl, aryl, or halogen).[13] His reason for doing so is that an increase of 200 Å in the maximum ultraviolet absorption of *n*-butyryl bromide is observed when it forms a complex with aluminium bromide, compared with the similar but greater increases of 700 and 400 Å shown by acetophenone and benzophenone respectively. The heats of formation of these substances with aluminium bromide show a similar relation and it was concluded that co-ordination of aluminium by oxygen had occurred. The proposed formula, however, implies a rate expression into which the halide enters as the square of its concentration, not found experimentally; but apart from this it seems almost certain that co-ordination of the type envisaged must lead to deactivation; otherwise acetophenone should afford a carbonium ion reactive in the Friedel–Crafts reaction. The lower bathochromic effect noticed with butyryl chloride may be the consequence of weaker interaction, *i.e.*, incomplete deactivation, and direct evidence of this can be obtained from Olivier's paper.[6] In the presence of a slight excess of benzoyl bromide, the rate at which benzophenone was produced was dependent on the concentration of the complex ($R{\cdot}COBr,AlBr_3$) though the order is not simple. A slight molecular excess of the catalyst accelerated the reaction considerably, the increase in rate being proportional to the concentration of this excess.* The constant for the reaction could therefore be calculated

* Similar observations by Ulich and Fragstein [20] are not comparable since these authors employed crystalline aluminium chloride and their reaction took place in a heterogeneous medium.

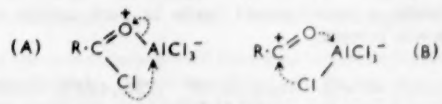
[20] Ulich and Fragstein, *Ber.*, 1939, **72**, 620.

from $k = k' + k''[AlBr_3]$, where k' refers to the experimentally determined constant for a given concentration of complex, and $k''[AlBr_3]$ to the increment associated with the excess of catalyst. The reversibility of the reaction $R{\cdot}COBr + AlBr_3 \rightleftharpoons R{\cdot}COBr,AlBr_3$ was not a factor influencing the reaction because the addition of one molecular equivalent of *m*-nitrobenzenesulphonyl chloride neither affected the rate nor led to the production of the phenyl sulphone. Thus the deactivating influence of the acid bromide evident in Table 8 which has been constructed from data selected from Olivier's paper must be due to that co-ordination to which Lebedev attributes the catalytic properties of aluminium halides.

TABLE 8. *Deactivation of the benzophenone reaction by benzoyl bromide (Olivier [7]).*

[Ph·COBr] (mole/l.)	0·100	0·200	0·330
[$AlBr_3$] ,,	0·285	0·330	0·300
10^3k_1 (min.$^{-1}$)	5·67	4·70	0·60

The slight tendency (Table 1) for the rate constant to increase with decreasing proportions of acid halide and the more pronounced deactivation in the case of pivalic anhydride are in harmony with this view. The essential feature of all Friedel–Crafts reactions, including elimination of carbon monoxide from tertiary acid derivatives, is the carbonium ion resulting from the polarisation of the carbon–halogen link or its equivalent. The incomplete deactivation discussed above may be ascribed to resonance between the



structures (A) and (B). These would be intermediates which, though relatively inactive as acylating agents, would, in the case of tertiary and certain other acid derivatives, be inherently unstable, the rate of decomposition being dependent on the nature of R.

EXPERIMENTAL

Qualitative Reaction between Pivaloyl Chloride and Benzene in the Presence of Anisole.—A mixture of pivaloyl chloride (7·07 g., 0·326 mole/l.), anisole (1·367 g., 0·063 mole/l.), and aluminium chloride (1·513 g., 0·063 mole/l.), dissolved in a mixture of benzene (160 c.c.) and nitrobenzene (20 c.c.), was stirred for 8 hr. at 20°, then decomposed by dilute sulphuric acid. Pivalic acid (1·25 g.) was removed by dilute alkali, and the dried benzene layer fractionated. After removal of the lower-boiling constituents (benzene, anisole, *tert.*-butylbenzene, and nitrobenzene) the residual liquid, b. p. 140°/12 mm. (1·05 g., ~12% based on the unrecovered pivaloyl chloride), was identified as *p*-methoxypivalophenone. The semicarbazone, m. p. 161° (Found: C, 62·4; H, 7·4; N, 17·2. Calc. for $C_{13}H_{19}O_2N_3$: C, 62·6; H, 7·6; N, 16·9%), melted 10° higher than that described by Rothstein and Saville [4] but a mixture of the two had an intermediate m. p.

Condensation of Pivaloyl Chloride with Toluene in Carbon Disulphide.—A solution of the acid chloride (6 g., 0·05 mole) in carbon disulphide was added during 30 min. to a stirred mixture of toluene, aluminium chloride (20 g., 0·15 mole), and carbon disulphide at 0°. After 15 min. the temperature was allowed to rise to 18° and stirring continued for a further 30 min. Ice and dilute sulphuric acid were added to the liquid, which was then extracted with ether; the ethereal solution was dried ($CaCl_2$) and fractionated, the products being those described by Rothstein and Saville.[4] The quantity of toluene used in three experiments, the results of which are given in Table 5, were 9·2 g. (0·10 mole), 18·4 g. (0·20 mole), and 46·0 g. (0·50 mole) respectively. In each case the total volume was adjusted to 100 c.c. with carbon disulphide.

Kinetic Measurements.—Details of some typical runs were given in Part VIII. An example of a determination by the titration method where equal concentrations of acid chloride and catalyst were used, is experiment H7.

Expt. H7. Titration method. Temp. 20·0°. [CMe_2·COCl] = [$AlCl_3$] = 0·10 mole/l.

Time (min.)	0	16	46·5	90·5	180	360·5	1260
[CMe_2·COCl] (mole/l.)	0·090	0·077	0·066	0·055	0·037	0·022	0·017

10^3k_1 = 0·439 min.$^{-1}$.

Examples of kinetic measurements in the presence of anisole are given in experiments *C* and No. 41. In each case the concentrations were: $[CMe_3 \cdot COCl] = 0.326$ mole/l., $[AlCl_3] = [PhOMe] = 0.063$ mole/l.

Expt. C. Titration method. Temp. 20·0°.

Time (min.)	$[CMe_3 \cdot COCl]$ (mole/l.)	Time (min.)	$[CMe_3 \cdot COCl]$ (mole/l.)	Time (min.)	$[CMe_3 \cdot CPCl]$ (mole/l.)	Time (min.)	$[CMe_3 \cdot COCl]$ (mole/l.)
0	0·184	90	0·156	263	0·131	500	0·110
11	0·180	169	0·142	361	0·120	1321	0·084
31	0·174						

Expt. 41. Carbon monoxide method. Temp. 20·36°.

Time (min.)	CO (mole/l.) (corr.)	$[CMe_3 \cdot COCl]$ (residual) (mole/l.)	$10^3 k_1$ (min.$^{-1}$)	Time (min.)	CO (mole/l.) (corr.)	$[CMe_3 \cdot COCl]$ (residual) (mole/l.)	$10^3 k_1$ (min.$^{-1}$)
0	0	0·326	—	180	0·0501	0·276	0·092
30	0·0139	0·312	0·146	210	0·0538	0·272	0·086
60	0·0242	0·302	0·127	240	0·0570	0·269	—
90	0·0325	0·294	0·115	270	0·0599	0·266	—
120	0·0396	0·286	0·109	300	0·0617	0·264	—
150	0·0454	0·281	0·098				

$10^3 k_1$ (by extrap.) = 0·168 min.$^{-1}$.

Experiment 46 illustrates a measurement made in pure carbon tetrachloride. Neither benzene nor nitrobenzene was present.

Expt. 46. Carbon monoxide method. Temp. 20·36°. $[CMe_3 \cdot COCl] = 0.326$ mole/l. $[AlCl_3] = 0.063$ mole/l.

Time (min.)	CO (mole/l.) (corr.)	$[CMe_3 \cdot COCl]$ (residual) (mole/l.)	$10^3 k_1$ (min.$^{-1}$)	Time (min.)	CO (mole/l.) (corr.)	$[CMe_3 \cdot COCl]$ (residual) (mole/l.)	$10^3 k_1$ (min.$^{-1}$)
30	0·0150	0·311	0·157	150	0·0699	0·256	0·161
60	0·0306	0·295	0·164	180	0·0807	0·245	0·158
90	0·0448	0·281	0·164	210	0·0904	0·235	0·155
120	0·0579	0·268	0·163				

Decomposition of Pivaloyl Chloride in Pure Nitrobenzene.—The following results with initial concentrations $[CMe_3 \cdot COCl] = 0.315$ and $[AlCl_3] = 0.063$ mole/l. are illustrative.

(*a*) At 174·8 min. a solution of aluminium chloride in nitrobenzene was added, the concentrations then being $[CMe_3 \cdot COCl] = 0.083$ mole/l., $[AlCl_3] = 0.133$ mole/l.

Time (min.)	2·5	10·1	31·5	77·1	168	178·6	187	200	245
Acid reacted (%)	58	63	63	70	71	79	85	90	95

(*b*) At 58 min. the concentration of the acid chloride was raised to 0·358/mole/l.

Time (min.)	0	9·5	30	58·1	64·3	88	188
Acid reacted (%)	56	69	69	69	77	77	77

Kinetic Runs with Pivalic Anhydride.—(a) *Titration method.* One molecule of anhydride affords one molecule of carbon monoxide and one of acid. Hence, if the initial concentration of pivalic anhydride is a, and the amount transformed in time t is x, the acid found by titration $y = [2(a - x) + x]$ and the unchanged anhydride $(a - x) = (y - a)$. For this experiment, with $[(CMe_3 \cdot CO)_2O] = 0.0473$ mole/l. and $[AlCl_3] = 0.125$ mole/l. at 20·0°, the results were as tabulated:

Time (min.)	$[CMe_3 \cdot CO_2H]$ (y) (mole/l.)	$[(CMe_3 \cdot CO)_2O]$ $(a - x)$ (mole/l.) *	$10^3 k_1$ (min.$^{-1}$)	Time (min.)	$[CMe_3 \cdot CO_2H]$ (y) (mole/l.)	$[(CMe_3 \cdot CO)_2O]$ $(a - x)$ (mole/l.) *	$10^3 k_1$ (min.$^{-1}$)
0	0·0932	0·0459	—	137·3	0·0687	0·0214	0·496
6·2	0·0883	0·0410	—	210·4	0·0615	0·0142	0·520
18·7	0·0854	0·0381	0·590	361·4	0·0533	0·0060	0·542
54·8	0·0791	0·0318	0·526	500·0	0·0533	0·0060	—

* After the initial rapid reaction, the slope of the curve log $(a - x)$–t is given by $\log (a - x) = 2.626 - 0.0023t$, whence the average value, $10^3 k_1 = 0.530$ min.$^{-1}$.

(b) ***Carbon monoxide method.*** One molecule of anhydride yields one molecule of carbon monoxide and thus resembles the acid chloride. Some results are recorded, for expts. 44 and 45.

Time (min.)	[CO] (mole/l.) (corr.)	$[(CMe_2{\cdot}CO)_2O]$ (residual) (mole/l.)	10^2k_1* ($min.^{-1}$)	Time (min.)	[CO] (mole/l.) (corr.)	$[(CMe_2{\cdot}CO)_2O]$ (residual) (mole/l.)	10^2k_1 ($min.^{-1}$)
	Expt. 44. $[(CMe_2{\cdot}CO)_2O]$ = 0·05 mole/l.			$[AlCl_3]$ = 0·125 mole/l.		Temp. 20·36°.	
0	0	0·0500	—	105	0·0253	0·0247	0·704
15	0·0038	0·0462	—	120	0·0279	0·0221	0·708
30	0·0082	0·0418	—	135	0·0303	0·0197	0·719
45	0·0123	0·0377	0·692	150	0·0323	0·0177	0·718
60	0·0161	0·0339	0·697	165	0·0344	0·0156	0·728
75	0·0195	0·0305	0·700	180	0·0362	0·0138	0·738
90	0·0225	0·0275	0·702	195	0·0378	0·0122	0·749

* For nearly 60% of the reaction, the slope was obtained from the expression, $\log(a - x) = \bar{2}{\cdot}7125 - 0{\cdot}0030kt$, from which the average $10^2k_1 = 0{\cdot}700$ $min.^{-1}$.

	Expt. 45. $[(CMe_2{\cdot}CO)_2O]$ = 0·05 mole/l.			$[AlCl_3]$ = 0·250 mole/l.		Temp. 20·36°.	
0	0	0·0500	—†	42	0·0362	0·0138	3·39
6	0·0046	0·0454	—	48	0·0389	0·0111	3·40
12	0·0123	0·0377	—	54	0·0413	0·0087	3·54
18	0·0189	0·0311	—	60	0·0431	0·0069	3·59
24	0·0244	0·0256	3·26	75	0·0466	0·0034	3·75
30	0·0289	0·0211	3·24	90	0·0489	0·0011	4·52
36	0·0329	0·0171	3·33				

† Calculated from $\log(a - x) = 2{\cdot}768 - 0{\cdot}0151t$. Average $10^2k_1 = 3{\cdot}48$ $min.^{-1}$.

The upward drift of the rate constant with time is in obvious contrast to the gradual reduction in the case of the acid chlorides. The above equations for $\log(a - x)$ were calculated by the method of least squares, using the data from 15 to 105 and from 6 to 54 min. respectively.

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877. *The Thermodynamics of the Formation of Complex Ions of Ethylenediaminetetra-acetic Acid and Bivalent Cations.*

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Calorimetric measurements have been made of the heats of formation of the complex ions of ethylenediaminetetra-acetic acid (EDTA) with nine bivalent cations. The values obtained refer to solutions of known and comparatively small ionic strength and are considered to be more accurate than any previously published figures. They have been combined with stability-constant data to give the entropy change for the formation of the complex ion. The sum of this entropy change and the standard entropy of a metallic ion is neither constant nor shows a steady change with increasing size of the metallic ion. Possible reasons for this are considered. The values of the heats and entropies of formation of the complexes are also discussed in the light of what is known of the interaction of the cations with ethylenediamine molecules and with acetate ions.

Some experiments have been carried out on copper, nickel, and zinc in solutions of higher pH in which appreciable quantities of hydroxy-complexes of the type $MY(OH)^{3-}$ are formed, where Y is the anion of EDTA. From these experiments approximate quantitative inferences have been drawn about the thermodynamics of the formation of such hydroxy-complexes.

THE property possessed by ethylenediaminetetra-acetic acid (EDTA) of forming stable complexes with many metallic ions has important practical consequences, in both analytical and applied chemistry. In addition, the equilibria between the complexes and the free EDTA anions and the metallic ions have considerable physicochemical interest. This paper deals with the thermodynamics of the equilibria for the following bivalent cations: magnesium, calcium, strontium, barium, nickel, copper, zinc, cadmium, lead.

Schwarzenbach and his collaborators [1] have measured accurately the formation constants for the complex ions MY^{2-} in the reaction

$$M^{2+} + Y^{4-} \rightleftharpoons MY^{2-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where Y^{4-} is the EDTA anion, *i.e.*,

$$(O_2C{\cdot}CH_2)_2N{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_2{\cdot}CO_2)_2^{4-}$$

These formation constants were determined at 20° and at an ionic strength of 0·1. We have determined calorimetrically the heats of formation (ΔH_f) of the ions MY^{2-} for the metals listed. Hence it has been possible to evaluate the entropy changes for reaction (1). When the thermochemical experiments were begun, the only values available for ΔH_f were those obtained by Carini and Martell [2] for the alkaline-earth metals from the temperature variation of the formation constants over a range of 30°. Values so obtained are usually less reliable than those determined directly. While our work was in progress, Charles [3] published the results of calorimetric measurements at 25° of ΔH_f for all the metals we have studied, and for some others. The precision aimed at in his measurements was not as high as we have attempted to achieve. Moreover, we have paid rather more careful attention to the experimental conditions. It was highly desirable to make the conditions as nearly as possible the same as those under which the formation constants were determined. This requires that the ionic strength should be controlled, and also that the concentrations of EDTA should be made as low as is consistent with the generation of temperature changes on the formation of the complex which are still large enough for accurate measurement. It is also necessary to control the pH of the solutions, since, as Schwarzenbach's work has shown, at high and low pH values complexes other than MY^{2-} can be formed, namely, complexes of the type MHY^{-} at low pH values and of the type $M(OH)Y^{3-}$ at high. For some metals, *e.g.*, barium, the range of pH values over which the formation of the hydrogen and hydroxy-complexes can be disregarded is very limited.

Experimental

The calorimeter used was that described by Davies, Singer, and Staveley.[4] The metal was contained in the calorimeter in about 1 l. of an approximately 0·01M-solution, and the small bottle within this held a known quantity of a relatively concentrated solution of the tetrapotassium salt of EDTA which contained about 10% more of this salt than that stoicheiometrically required for complete complex-formation of the metal ions. The temperature change, which was usually between 0·05° and 0·10°, was measured with a resistance thermometer, and the associated quantity of heat evolved or absorbed deduced from this by the usual calibration experiments carried out with electrical heating. All measurements were made at 20°.

Although we have used metal and EDTA concentrations considerably smaller than those employed by Charles, they are nevertheless much higher than those used by Schwarzenbach in the determination of the stability constants of the complexes. Since complex formation involves combination of ions of opposite charge, this means that there is an appreciable change in ionic strength accompanying this process. In our experiments, a constant background concentration of neutral salt was maintained by making both the metal solutions and the more concentrated solutions of the complexing agent always 0·1N in potassium nitrate. The final ionic strength μ in a complex-forming experiment was approximately 0·17. We shall present our results in such a way that μ can be exactly estimated in any particular case.

As will be shown, it was necessary in our work to use the third and fourth dissociation constants of EDTA, and although these have been determined by Schwarzenbach and Ackermann,[5] and by Carini and Martell,[6] it seemed advisable to measure them ourselves at the ionic strength

[1] Schwarzenbach, Gut, and Anderegg, *Helv. Chim. Acta*, 1954, **37**, 937.
[2] Carini and Martell, *J. Amer. Chem. Soc.*, 1954, **76**, 2153; Schwarzenbach and Ackerman, *ibid.*, 1947, **30**, 1798.
[3] Charles, *ibid.*, p. 5854.
[4] Davies, Singer, and Staveley, *J.*, 1954, 2304.
[5] Schwarzenbach and Ackerman, *Helv. Chim. Acta*, 1947, **30**, 1798.
[6] Carini and Martell, *J. Amer. Chem. Soc.*, (*a*) 1952, **74**, 5745; (*b*) 1953, **75**, 4810.

of our calorimetric experiments. Since we need to calculate the actual amounts of the ions of EDTA from pH readings obtained with a glass electrode, we need to know the "hybrid" ionisation constants:

$$K_3 = \{H^+\}[HY^{3-}]/[H_2Y^{2-}] \text{ and } K_4 = \{H^+\}[Y^{4-}]/[HY^{3-}]$$

where $-\log_{10}\{H^+\}$ is the pH measured with the glass electrode. These constants were obtained by making pH measurements during the titration of pure EDTA with a standard carbon-dioxide-free potassium hydroxide solution made by shaking carbon dioxide-free potassium chloride solution with silver oxide.[7] These titrations were carried out at such concentrations and in the presence of so much potassium nitrate that μ reached the desired value when the pH became pK for the ionisation constant under investigation. The average results obtained from several experiments for the hybrid ionisation constants K_3 and K_4 at 20° were as follows: $pK_3 = 6{\cdot}23$ at $\mu = 0{\cdot}184$ and 6·23 at $\mu = 0{\cdot}147$; $pK_4 = 10{\cdot}21$ at $\mu = 0{\cdot}234$ and 10·27 at $\mu = 0{\cdot}175$. Values of pK_4 at the slightly different ionic strengths encountered in the calorimetric experiments were obtained from these values by assuming a linear relation between pK_4 and μ[1]. Owing to hydrolysis, to calculate K_4 from the titration curve it is necessary to have a value for the hybrid ionic product of water at 20°, this quantity being the product of the hydrogen-ion activity and hydroxyl-ion concentration, at a known ionic strength. (A knowledge of this ionic product is also necessary in working out the ionic composition of the solutions later designated as solutions B.) From experiments on solutions containing known amounts of carbonate-free alkali this hybrid ionic product was found to be $1{\cdot}23\ (\pm 0{\cdot}09) \times 10^{-14}$ at 20° and $\mu = 0{\cdot}213$.

Potassium nitrate was preferred to potassium chloride as a neutral salt since the tendency of transition-metal ions to form ion pairs or complexes is smaller with the nitrate ion than with the chloride ion. In the experiments with lead, however, since there is some evidence that this metal forms complexes with nitrate ions,[8] potassium perchlorate was used instead. For each metal a concentrated solution in 0·1M-potassium nitrate of one of its pure salts was prepared and analysed for its metal content. For magnesium, cadmium, copper, nickel, and zinc, sulphates were used, for barium and calcium the chlorides, for strontium the nitrate, and for lead the perchlorate. All these solutions except that containing magnesium were analysed gravimetrically. Cadmium and zinc were determined as their 8-hydroxyquinoline complexes, strontium and barium as the sulphates, lead as the chromate, nickel as the dimethylglyoxime derivative, copper by electrolytic deposition, and calcium by precipitation of the oxalate followed by ignition to carbonate. The magnesium content of the magnesium sulphate solution was estimated by titration, with eriochrome-black as indicator, against an EDTA solution which had been standardised against standard calcium and zinc solutions. The solutions of copper, nickel, and zinc were made 0·02N with sulphuric acid to repress hydrolysis. The lead perchlorate solution contained a known excess of perchloric acid for the same reason.

To prepare a metal solution for a calorimetric experiment a known weight of the concentrated solution was mixed with 941·5 ml. of a carbon dioxide-free solution of 0·1M-potassium nitrate in the calorimeter, and a few ml. of 0·5N-nitric acid added. The resulting solution will be referred to as solution A. The precise amount of 0·5N-nitric acid added in any particular case was that which trial experiments had shown would lead to a suitable final pH after the addition of the EDTA to solution A. Except in the experiments with lead, the concentrations of the metals in solutions A were approximately 0·01M. With lead, where potassium perchlorate was used instead of potassium nitrate, to avoid precipitation of potassium perchlorate on the addition of the EDTA the concentrations of the lead and the complexing agent were reduced to about half their usual values.

As the sodium ion forms complexes with EDTA while the potassium ion does not, we have preferred to use the tetrapotassium rather than the tetrasodium salt and make a correction, as Charles did. The commercial acid was dissolved in carbonate-free potassium hydroxide, the solution filtered, and the acid then slowly reprecipitated from dilute solution by adding an equivalent quantity of nitric acid. The precipitate was washed and then the whole process was repeated once. The purified acid so obtained was then dissolved in carbonate-free potassium hydroxide in 0·1M-potassium nitrate, about 5% more alkali being used than was just required for complete formation of the tetrapotassium salt. We shall call this solution B.

In order to determine ΔH_f for the reaction (1) a minimum of two calorimetric experiments

[7] Schwarzenbach and Biedermann, *Helv. Chim. Acta*, 1948, **31**, 331.
[8] Bale, Davies, and Monk, *Trans. Faraday Soc.*, 1956, **52**, 816.

was required. The first consisted in measuring the heat absorbed, ΔH_C, when a known amount (about 21 ml.) of solution B was added to the solution A to give a final solution C. Immediately solution C was removed from the calorimeter its pH (pH_C) was measured at 20° by using a glass electrode and a "Cambridge" pH meter. The second experiment consisted in measuring the heat absorbed ΔH_D when exactly the same amount of solution B was added to a solution containing none of the metal but otherwise identical with solution B and therefore containing the same amount of free acid. The pH (pH_D) of this second final solution (D) was also measured. The successive dissociation constants of EDTA being known, the ionic composition of solution D was estimated. Even when pH_D was between 10 and 11 (when solution D contained a considerable quantity of hydroxyl ion), owing to the very small value of the fourth dissociation constant, while most of the complexing reagent was present as the Y^{4-} ion, some 20—30% was there as HY^{3-}. (The amount present as H_2Y^{2-} in solution D was always negligible.) Likewise, for solution C, pH_C, the formation constant of MY^{2-}, and the total amounts of metal and complexing agent being known, it was possible to calculate the ionic composition. Conditions were so chosen that at pH_C the metal was virtually completely in the form of the complex MY^{2-}. (With copper, nickel, and zinc a rather more extended series of experiments was carried out to investigate the behaviour at high pH.) The surplus complex-forming agent at pH_C was usually present mostly as HY^{3-} with small amounts of Y^{4-} and H_2Y^{2-}. The difference $\Delta H_C - \Delta H_D$ gives the heat-content change ΔH_2 for the process

$$M^{2+} + H^+_D + Y^{4-}_D + HY^{3-}_D + OH^-_D \longrightarrow MY^{2-}_C + Y^{4-}_C + HY^{3-}_C + H_2Y^{2-}_C + OH^-_C + H^+_C \quad . \quad (2)$$

Since the amounts of all the ions in process (2) are known, the quantity sought, ΔH_f, can be evaluated from ΔH_2 by allowing for the heat-content changes due to the following processes:

$$H^+ + HY^{3-} \rightleftharpoons H_2Y^{2-} \quad +\Delta H_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$H^+ + Y^{4-} \rightleftharpoons HY^{3-} \quad +\Delta H_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$H^+ + OH^- \rightleftharpoons H_2O \quad +\Delta H_5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

For ΔH_3 and ΔH_4 we have used the values Carini and Martell [6(b)] derived from the temperature variation of the dissociation constants, and for ΔH_5 the value of 13,610 cal. calculated for 20° from Pitzer's formula.[9]

The thermal capacity of the calorimeter was virtually the same for all experiments so that once it had been established it was not necessary to determine the electrical energy equivalent after each measurement, though check determinations were made from time to time.

Results.—The unit in which all results are expressed is the thermochemical calorie (= 4·1833 international joules = 4·1840 absolute joules). The accuracy of which the calorimeter is capable has been discussed in a previous paper.[4] In favourable cases it can reach 0·1%, but this has not been achieved here, since to keep the ionic strength down it was necessary to work with comparatively dilute solutions. We consider that our average ΔH_f value for any one metal is reliable to ±150 cal./mole, though the limits of accuracy are not easy to assess, since a value of ΔH_f depends not only on the thermal, pH, and quantity measurements but also on the values adopted for the third and fourth ionisation constants of EDTA appropriate to the ionic strength used and on the heat-content changes associated with these ionisation stages. Our results are accordingly presented in Tables 1 and 2 in sufficient detail to permit recalculation from them of ΔH_f by use of different values for the ionisation constants and associated heats of ionisation, should these be revised by later work.

There were slight variations from one metal to another in μ for the solutions C, depending on which salt of the metal was used. For the C solutions containing magnesium, cadmium, copper, nickel, and zinc, μ was between 0·173 and 0·177, while for solutions of barium, calcium, and strontium, μ was 0·165. For the D solutions, μ was between 0·210 and 0·213. For lead, μ for solutions C and D was 0·133 and 0·157 respectively.

Some experiments were also carried out with copper, zinc, and nickel in which the final solution had a sufficiently high pH to contain appreciable quantities of the so-called hydroxy-complexes of the type $M(OH)Y^{3-}$. The results of these experiments are recorded in Table 2.

[9] Pitzer, *J. Amer. Chem. Soc.*, 1937, **59**, 2365.

TABLE 1.

Type *		M	pH	Q	ΔH_f
C		9·530 Mg^{2+}	8·91	7·59	+3·15
C		9·510 Mg^{2+}	8·97	7·69	+3·14
C		9·425 Ca^{2+}	8·15	97·09	−6·45
C	K_4Y = 10·70	9·395 Ca^{2+}	7·86	96·30	−6·45
C	V = 982	9·312 Ba^{2+}	8·82	81·43	−4·86
C		9·343 Ba^{2+}	9·14	81·14	−4·83
D			10·84, 10·86,	29·91, 29·42,	
D			10·85, 10·85	29·94, 29·71	
C		9·948 Sr^{2+}	9·13	79·53	− 4·12
C		9·970 Sr^{2+}	8·94	79·34	− 4·09
C	K_4Y = 11·20	9·789 Cd^{2+}	8·62	135·03	−10·04
C	V = 982	9·793 Cd^{2+}	7·77	135·26	−10·08
D			10·87, 10·91	31·45, 31·71	
C		9·418 Zn^{2+}	8·36	94·58	− 5·68
C		9·341 Zn^{2+}	9·10	93·04	− 5·61
C	K_4Y = 11·32	9·546 Ni^{2+}	7·60	120·85	− 8·31
C	V = 982	9·553 Ni^{2+}	7·38	121·03	− 8·39
D			10·82, 10·71	35·15, 36·47	
C	K_4Y = 10·93	9·790 Cu^{2+}	6·16	123·27	− 8·84
D	V = 981		10·76	31·70	
C	K_4Y = 10·97	9·761 Cu^{2+}	6·23	138·09	− 8·78
D	V = 984		10·78	48·41	
C	K_4Y = 10·93	9·699 Cu^{2+}	7·38	116·96	− 8·68
C	V = 980	9·770 Cu^{2+}	7·60	116·88	− 8·53
D			10·84, 10·91	27·24, 27·17	
C	K_4Y = 10·97	9·643 Cu^{2+}	9·26	130·03	− 8·53
D	V = 983		10·94	43·02	
C		4·982 Pb^{2+}	9·75	88·31	−13·94
C	K_4Y = 5·495	5·100 Pb^{2+}	8·17	90·69	−14·19
C	V = 982	5·100 Pb^{2+}	9·45	90·43	−13·99
D			10·74, 10·74	11·74, 11·38	

* The letter C means that the experiment was the formation of the complex ion, while D denotes a dilution experiment (see text). K_4Y = no. of millimoles of the tetrapotassium salt of EDTA; V = total volume (ml.) after mixing or dilution; M = no. of mg. ions of metal; pH = pH of final solution; Q = heat evolved in calories on forming the solution C or D (two or more Q values given together are the results of separate experiments carried out under identical conditions); ΔH_f = calculated heat content change for the reaction $M^{2+} + Y^{4-} \rightleftharpoons MY^{2-}$ in kcal./mole (1 cal. = 4·1840 abs. joules).

TABLE 2.

Type		M	pH	OH^-	Q	ΔH_f	ΔH_s
C		9·809 Zn^{2+}	11·06	1·19	53·34	−5·67	0
C	K_4Y = 10·92	9·740 Zn^{2+}	10·94	1·57	52·45	−5·66	0
C	V = 977	9·848 Ni^{2+}	10·99	1·40	75·37	−7·89	+ 3·24
D			11·38, 11·44		−6·45, −6·68		
C	K_4Y = 10·93	9·825 Ni^{2+}	11·08	0·47	76·06	−7·82	+11·04
D	V = 973		11·34, 11·27		−6·55, −6·74		
C	K_4Y = 10·93	9·790 Cu^{2+}	9·83	0·33	111·81	−8·62	—
D	V = 978		10·99		20·97		
C	K_4Y = 10·93	9·773 Cu^{2+}	10·27	0·90	140·40	−8·98	− 3·37
D	V = 976		11·15		11·87		
C	K_4Y = 10·92	9·760 Cu^{2+}	10·81	1·89	85·82	−9·11	− 2·27
D	V = 977		11·38, 11·44		−6·45, −6·68		
C	K_4Y = 10·92	9·619 Cu^{2+}	10·83	1·96	82·83	−9·12	− 2·21
C	V = 977	9·730 Cu^{2+}	10·98	1·55	85·51	−9·22	− 3·45
D			11·40, 11·45		−7·89, −8·04		

For C, D, M, and K_4Y, see notes to Table 1; V = volume of solution in calorimeter, in ml., after mixing; pH = pH of the same solution; OH^- = number of mg.-ions of hydroxyl ion removed from the system as a result of complex formation; Q = observed heat evolved, in calories; ΔH_f = heat absorbed (cal.) per g.-ion of metal entering into complex formation; ΔH_s = estimated heat-content change for the reaction $MY^{2-} + OH^- \rightleftharpoons M(OH)Y^{3-}$ per mole of the last ion.

TABLE 3.

	(1) ΔH_f	(2) ΔG	(3) ΔS	(4) $S°$	(5) $\Delta S + S°$	(6) ΔH_f (ref. 3)	(7) ΔH_f (ref. 2)	(8) r
Mg	+ 3·14	−11·65	50·5	−28·2	22·3	+ 3·1, + 3·1	−2·9	0·66
Ca	− 6·45	−14·34	26·9	−13·2	13·7	− 5·8, − 6·5	−2·5	1·01
		−14·69	28·1		14·9			
Sr	− 4·11	−11·57	25·4	− 9·4	16·0	− 4·2, − 4·2	−4·1	1·18
Ba	− 4·83	−10·40	19·0	+ 3	22	− 5·1, − 5·3	−4·1	1·34
Ni	− 8·35	−24·96	56·7	—	—	− 7·6, − 7·8	—	0·69
Cu	− 8·67	−25·20	56·4	−23·6	32·8	− 8·2, − 8·4	—	0·72
Zn	− 5·61	−22·12	56·3	−25·45	30·8	− 4·5, − 4·9	—	0·74
Cd	−10·08	−22·07	40·9	−14·6	26·3	− 9·1, − 9·3	—	0·97
Pb	−14·08	−24·18	34·5	+ 5·1	39·6	−13·1, −13·4	—	1·20

(The units of ΔH_f and ΔG are kcal./g. ion, of ΔS cal./g.-ion deg., and of r, the ionic radius, Ångstrom units.)

DISCUSSION

In Table 3 are recorded: (1) our mean values for ΔH_f at 20° for the reaction $M^{2+} + Y^{4-} \longrightarrow MY^{2-}$; (2) the values of ΔG at 20° for this reaction calculated from Schwarzenbach's formation constants [1] for $\mu = 0{\cdot}1$; (3) the derived values of the entropy change, ΔS; (4) the standard entropies, $S°$, of the metal ions (taken from the National Bureau of Standards publication "Selected Values of Chemical Thermodynamic Properties," Washington, 1952); (5) values of the quantity $\Delta S + S°$; (6) the values of ΔH_f obtained by Charles at 25°, and (7) those given by Carini and Martell for 30°; and (8) the ionic radii of the metallic ions.[10]

It will be seen that Charles's results are in fair agreement with our own. The wider discrepancies between our figures and those of Carini and Martell exemplify the unreliability of ΔH values obtained by measuring stability constants over a limited temperature range. In particular, it will be noted that they give a ΔH value of the magnesium complex which is not even of the correct sign. As the quantity $\Delta S + S°$ will play a considerable part in the discussion of our results, we must draw attention to possible errors in the $S°$ values. From a survey of the data available for calculating ionic entropies, and having regard not only to the values given in the publication mentioned but also to those tabulated by other authorities (*e.g.* Kelley [11] and Latimer, Pitzer, and Smith [12]) it seems that some of the $S°$ values in Table 3 could be in error by as much as 2 e.u. Therefore the quantities $\Delta S + S°$ may be in error by 2—3 e. u.

As Charles, and Carini and Martell have pointed out, the stability of the EDTA complexes is due largely to the ΔS values which are large and positive owing to the liberation of solvent molecules previously in the hydration sphere of the component ions. If it were true for all the metals examined that, in their complexes, the EDTA ion was being fully utilised as a hexadentate ligand, then we would expect that these complexes would have essentially the same shape, differ relatively little in overall size, and hence interact with the surrounding water in much the same way. The entropy of the complex ion in solution would then be almost constant or at least show a comparatively gradual change with the radius of the metallic ion within it. The same statements would then apply to the quantity $\Delta S + S°$ since this only differs from the standard entropy of the complex ion by the constant entropy of the Y^{4-} ion. Charles suggested that the quantity $\Delta S + S°$ was in fact approximately constant by plotting ΔS against $S°$ and showing that the points conformed reasonably closely to a straight line. It is, however, clear from Table 3 that there are variations in $\Delta S + S°$ which are well outside any uncertainty in this quantity. Particularly striking is the difference in $\Delta S + S°$ for lead and strontium, two ions of approximately the same size, and also the fact that for the alkaline earths the values are neither constant nor show a simple trend with increasing size of metallic ion.

There are, however, a number of reasons for the absence of any simple regularity in the values of $\Delta S + S°$ and also of ΔH_f. We are concerned with the equilibrium

[10] Ahrens, *Geochim. Cosmochim. Acta*, 1952, **2**, 155; *Nature*, 1954, **174**, 644.
[11] Kelley, *U.S. Bur. Min. Bull.*, 1937, No. 406; 1949, No. 477.
[12] Latimer, Pitzer, and Smith, *J. Amer. Chem. Soc.*, 1938, **60**, 1829.

$M^{2+} + Y^{4-} \rightleftharpoons MY^{2-}$, in which all three ions are hydrated, and the changes in the thermodynamic functions for this reaction may be regarded as the relatively small differences between the much larger changes in these functions when a gaseous metallic ion becomes hydrated on the one hand and on the other becomes co-ordinated with the EDTA ion. If the metallic ion in solution is particularly closely associated with, say, six water molecules, each of these is a separate entity which can individually take up such a position as to minimise the free energy of the system. In the EDTA anion, by contrast, the positions of the six atoms available for co-ordination cannot be so freely altered, and a compromise must be reached in which probably none of these six atoms is in its optimum position in relation to the metal ion. The size of the central metallic ion must affect the degree to which the bonds of the EDTA anion are distorted in forming the complex, and this will also influence the distances between pairs of oxygen atoms in different carboxyl groups, between which there will be repulsion. If atomic models are used it appears that an octahedron is most nearly approached with metallic ions neither too big nor too small, and this may be chiefly why, with the alkaline earths, the complex formed with the greatest evolution of heat is that of calcium. It may also be noted that, just as for the pair magnesium–calcium, so also for the pair zinc–cadmium (for which the change in ionic radius is much the same), there is a considerable drop in ΔH (*i.e.*, the formation of the complex becomes more exothermic) on going from the smaller to the larger cation. On geometrical grounds alone, therefore, the relation between the size of metallic cation and the heat of interaction of this gaseous ion with the EDTA anion may be more complicated than the relation between ionic size and heat of hydration. A further factor which will militate against a smooth relation between the former heat of interaction and cationic radius is that with increase of the latter a point may be reached when the anion acts as a 5- rather than as a 6-co-ordinating unit, as is indeed suggested by the experiments of Wheelwright, Spedding, and Schwarzenbach [13] with the rare earths.

The thermodynamic properties of these complexes, however, can scarcely be determined by size factors alone. They must also depend upon the nature of the interaction between the metal ion and the nitrogen and oxygen atoms of the EDTA anion. For the alkaline-earth complexes we would expect that their interaction is essentially electrostatic, whereas for elements such as copper and nickel it will have a greater degree of covalent character. According to the use made of the lone pair of electrons of the nitrogen atoms, the angles between the orbitals on these atoms will vary, and this in turn will affect spatial relations within the complex. Thus, trials with models showed that it was easier to fit the two nitrogen and four oxygen atoms approximately octahedrally round the metal atom if the orbitals of the nitrogen atoms were given the directions of 4-covalent nitrogen, rather than that of 3-covalent nitrogen. (We may add that a secondary consequence of differences in the interaction between the metal atom and the ligands will be that the effective charges on the nitrogen and oxygen atoms in the complex will vary with the nature of the metal which in turn will affect the interaction of the complex with surrounding water molecules.) Furthermore, especially with metals whose complexes involve some degree of covalent bonding between metal and ligand, preference need not always be given to an octahedral complex. For example, since copper never appears to form really stable 6-co-ordinated complexes it would seem probable that in interacting with the EDTA anion it uses only four of the available six atoms, and so $\Delta S + S^\circ$ need not necessarily be the same for the copper complex as for the complex with a cation of about the same size but which co-ordinates with all six of the atoms available in the EDTA anion.

One approach by which the operation of some of these factors might be investigated is to consider the EDTA anion as consisting, as far as its complexing powers are concerned, of one ethylenediamine molecule and four acetate ions, and then to review the thermodynamics of EDTA complexes in the light of what is known about the interaction of the same metal ions with ethylenediamine and with acetate ions. Unfortunately, reliable data for ethylenediamine complexes exist only for copper, nickel, cadmium, and zinc.[14]

[13] Wheelwright, Spedding, and Schwarzenbach, *J. Amer. Chem. Soc.*, 1953, **75**, 4196.
[14] (*a*) Davies, Singer, and Staveley, ref. 4; (*b*) Poulsen and Bjerrum, *Acta Chem. Scand.*, 1955, **9**, 1407; (*c*) Spike and Parry, *J. Amer. Chem. Soc.*, 1953, **75**, 2726, 3770.

Although formation constants have been measured for ion pairs of an acetate ion and all of the cations of Table 3, only for magnesium, calcium, strontium, and barium have comparable measurements been made at more than one temperature, so that ΔH and ΔS are only known for these metals.[15]

For the copper ion, co-ordination of one ethylenediamine causes an evolution of heat of 13·0 kcal. per mole and an entropy increase of 5·4 (Poulsen and Bjerrum [14(b)]). Yet when this cation complexes with the EDTA anion, although the entropy increase is 57 e.u., the heat evolved is only 8·59 kcal., in spite of the fact that the copper ion [16] has a stronger tendency to form ion pairs with the acetate ion than any other metal in Table 3 except lead.[17] However, the values given by Bell and George [18] for ΔG, ΔH, and ΔS for ion pairs involving various anions other than the acetate ion show that ΔH is usually small and can be either positive or negative, while ΔS can vary considerably. Their results suggest that when ΔS is relatively large (leading to a ΔG which is also large numerically, but negative) the formation of the ion pair is endothermic. The results obtained by Nancollas [15] likewise show that a relatively high ΔS tends to be associated with a positive ΔH. When, therefore, the ΔG values for cation–acetate ion-pair formation (which are negative) are relatively large numerically (as for copper in particular) it may well be that the corresponding ΔS values are high, and this is primarily responsible for the large entropy increase when, say, the cupric ion forms complexes with the EDTA anion. It is possible, however, that ΔH for the ion-pair formation is positive, and that this to some extent offsets the exothermic interaction of the copper atom with the nitrogen atoms, thus causing the overall ΔH_f to be numerically less than that for the formation of a 1 : 1 copper–ethylenediamine complex. On this analysis, we might say that, roughly speaking, the heat evolved in the formation of the copper–EDTA complex arises from the reaction of the metal atom with the nitrogen atoms, while most of the entropy increase arises from the interaction with the acetate groups. Nevertheless, the observed entropy increases are larger than might be expected on this basis. Thus for the nickel–EDTA complex the heat evolved per mole is the same within 0·7 kcal. as the heat evolved when this cation co-ordinates with one mole of ethylenediamine. If this is taken to mean that for 1 : 1 ion-pair formation of the nickel ion and the acetate ion, ΔH is almost zero, it follows from the ΔG value for the ion-pair formation that the associated ΔS is only about 5 e.u., whereas for the EDTA complex of nickel the ΔS value is approximately 57 e.u. (For the 1 : 1 complex of nickel with ethylenediamine, ΔS is about 4 e.u.) It may be that in an EDTA complex desolvation is much more complete than for a simple ion pair, since in the former any one charged centre benefits from the screening effect of the rest of the EDTA ion. It would clearly be interesting to have some information about the thermodynamics, not only of ethylenediamine complexes and of metal–acetate ion-pair formation, but also of the interaction of metal ions with the anions of polycarboxylic acids.

The results recorded in Table 2 throw some light on the thermodynamics of the formation of hydroxy-complexes in solutions of higher pH. It will be seen that in these experiments appreciable quantities of hydroxyl ions were removed from the system, consequent on the reaction

$$MY^{2-} + OH^- \rightleftharpoons M(OH)Y^{3-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

or alternatively

$$MY(H_2O)^{2-} + OH^- \rightleftharpoons M(OH)Y^{3-} + H_2O$$

(In the experiments of Table 1, by contrast, the amount of hydrogen or hydroxyl ions which apparently disappeared was always zero within the limits of experimental error, showing that the formation of hydrogen- or hydroxy-complexes did not occur to any significant extent.)

[15] Nancollas, *J.*, 1956, 744.
[16] Lloyd, Wycherley, and Monk, *J.*, 1951, 1786; Sircar, Aditya, and Prasad, *J. Indian Chem. Soc.*, 1953, **30**, 833.
[17] Das, Aditya, and Prasad, *ibid.*, 1952, **29**, 169; Aditya and Prasad, *ibid.*, 1953, **30**, 213; Shin Suzuki, *J. Chem. Soc. Japan*, 1953, **74**, 531.
[18] Bell and George, *Trans. Faraday Soc.*, 1953, **49**, 619.

From the data in Table 2, estimates can be made of K_6, where

$$K_6 = [MY(OH)^{3-}]/([MY^{2-}][OH^-])$$

and of ΔH_6, the corresponding heat content increase. For copper, $\log_{10} K_6 = 2{\cdot}5 \pm 0{\cdot}1$, $\Delta H_6 = -2{\cdot}7 \pm 1$ kcal./mole; for zinc, $\log_{10} K_6 = 2{\cdot}1 \pm 0{\cdot}1$, $\Delta H_6 \simeq 0$; for nickel, $\log_{10} K_6 = 1{\cdot}8 \pm 0{\cdot}3$, $\Delta H_6 \simeq 3$kcal./mole. (Although these values are rather rough, particularly those of ΔH_6, it is obvious from Table 2 that the hydroxy-complex of copper is formed exothermically from the normal complex, while the same process for nickel is endothermic and that for zinc almost athermal.) This difference between copper and nickel is noteworthy since ΔH_f for these two metals is about the same. Differences also exist in the values of ΔS_6, the entropy increase associated with reaction (6). The above values of K_6 and ΔH_6 lead to a value of ~2 e.u. for ΔS_6 for the copper complex, and although this quantity cannot be so reliably estimated for zinc and nickel, it is clear that for zinc ΔS_6 is considerably larger than 2 e.u., and even bigger for nickel where ΔH_6 is positive. Finally, it seems very probable that for the normal MY^- complexes of tervalent metals one of the six co-ordinating positions is occupied by a water molecule. Of the bivalent metals we have studied, the same may well be true of copper, at least, in view of its well-known reluctance to form hexa-co-ordinated complexes. If this is so, the formation of the hydroxy-complex really arises from the process

$$Cu(H_2O)Y^{2-} + H_2O \rightleftharpoons Cu(OH)Y^{3-} + H_3O^+ \quad . \quad . \quad . \quad . \quad (7)$$

and the value of $\Delta H_6 = -2{\cdot}7$ kcal./mole then leads to a value of $\Delta H_7 = 10{\cdot}9$ kcal. for the heat content increase in process (7), that is, for the heat of ionisation of the bound water molecule.

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878. *The Sulphates and Selenate of Polonium.*

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A basic sulphate and selenate, $2PoO_2{,}SO_3$ and $2PoO_2{,}SeO_3$, and a disulphate, $Po(SO_4)_2$, have been prepared; the disulphate probably forms a series of hydrates. The solubilities of these compounds in sulphuric and selenic acid have been investigated. Unstable compounds analogous to the tellurium and selenium derivatives are formed from polonium metal and sulphur trioxide or selenium trioxide.

STUDIES of the diffusion,[1] electrochemical,[2,3] and solvent-extraction [4] behaviour of polonium as tracer in sulphuric acid solution appear to indicate the formation of complex ions in solution, but there are no data on the composition of the species involved. We have therefore attempted to fill certain gaps in our knowledge of these compounds.

Polonium Disulphate.—The hydrated disulphate is obtained as a white solid by treating solid polonium tetrachloride or " hydroxide " with sulphuric acid (0·5—5·0N); removal of the supernatant liquid leads to a series of irreversible colour changes at room temperature; these are also observed on heating (pink at 200°, deep purple at 380°) and are probably due to progressive dehydration. The hydrate (or hydrates) can also be efficiently dehydrated by washing with anhydrous ether. It was not possible to obtain *X*-ray powder photographs of the hydrates owing to the spontaneous dehydration; the capillaries usually

[1] Servigne, *J. Chim. phys.*, 1934, **31**, 147, 211.
[2] Guillot and Haissinsky, *Compt. rend.*, 1934, **198**, 1758.
[3] Haissinsky, *ibid.*, 1932, **195**, 131.
[4] Cairo, Geneva Conference 1955, Paper A/Conf.8/P/1028.

exploded within a few hours of preparation, probably owing to the pressure of radiolytic gas formed within the capillary. The powder photographs of the anhydrous compound were complex and have not been indexed.

The anhydrous salt is stable to above 400° and decomposes to the dioxide at about 550°. The disulphates are insoluble in acetone or ethyl alcohol and may be hydrolysed by the latter; they are very soluble in dilute hydrochloric acid.

The disulphate is of particular interest since no tellurium analogue is known and the formation of this compound is evidence for the increased basicity of quadrivalent polonium which is to be expected from its position in the Periodic Table.

Basic Polonium Sulphate.—Analyses of this compound gave a value of 2·06 ± 0·05 for the ratio Po : SO_3. The *compound* is presumably $2PoO_2,SO_3$, analogous to the only known tellurium sulphate, $2TeO_2,SO_3$. Like tellurium sulphate, it gave very poor *X*-ray powder photographs. It is formed as a white solid (yellow above 250°) in the same way as the disulphate but with more dilute sulphuric acid (0·02—0·25N). It may also be formed by the hydrolysis of the disulphate. It is stable to above 400° and decomposes to the dioxide at about 550°. Specimens which were dried at 380° in *X*-ray capillaries were quantitatively converted into the disulphate; this is apparently due to the relatively high concentration of sulphuric acid vapour in the capillary as compared with the 1-cm. diameter filter sticks used for the analytical preparations. Samples for *X*-ray powder photography were therefore prepared as for analysis and transferred to the capillary by means of a microglass spatula.

The basic sulphate is more soluble in dilute sulphuric acid than the disulphate and is readily soluble in dilute hydrochloric acid.

Basic Polonium Selenate.—Analyses gave a value of 1·96 ± 0·16 for the ratio Po : SeO_3 and the *compound* is presumably $2PoO_2,SeO_3$. It is a white solid (deep yellow above 250°) and appears to be stable to above 400°. It is formed by treating polonium tetrachloride or " hydroxide " with selenic acid (0·015—5·0N) and is very soluble in dilute hydrochloric acid.

Bivalent Polonium Sulphate.—Polonium as tracer in sulphuric acid solution is reported to be reduced by hydroxylamine at the boiling point.[7,8] Work with milligram amounts of polonium confirms these observations, since suspensions of the disulphate in sulphuric acid (1—2N) dissolve when boiled with hydroxylamine, yielding a pink solution; this colour appears to be characteristic of bivalent polonium. The quadrivalent sulphate is reprecipitated on cooling after some minutes, even in the presence of excess of hydroxylamine.

A knowledge of the reducing reaction involved and its redox potential would be of value since the potential could be equated to the Po(IV)–Po(II) redox potential.

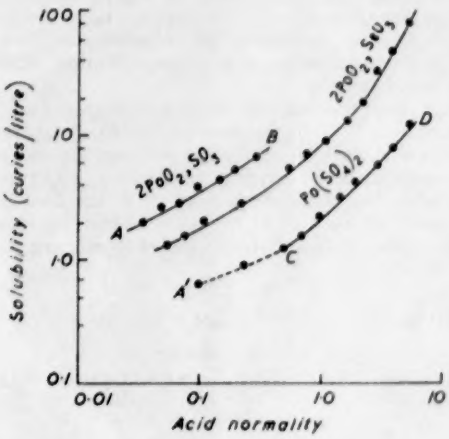
Solubility Data.—The dependence of the solubilities of the sulphates and selenate upon the respective acid concentrations are expressed graphically in the Figure. The basic sulphate appears to be metastable since the solubility curve of the disulphate (*D*) can be extended to regions of lower acid concentration by diluting the acid in contact with solid polonium disulphate to concentrations at which the basic sulphate is normally formed (*A'*); further, seeding the aqueous phase in contact with the basic sulphate with small crystals of the disulphate decreases the solubility to a marked degree. Determinations made at sulphuric acid concentrations between 0·3 and 0·5N gave erratic results. The increase in solubility with acid concentration appears to indicate complex-ion formation, but no simple relationship could be deduced.

The solubility curve for the basic selenate in selenic acid does not show the discontinuity found for the sulphates; it is possible that the diselenate is formed at high acidities, but attempts to prepare the compound by evaporation of solutions of the basic selenate in concentrated selenic acid were unsuccessful.

Polonium Sulphotrioxide and Selenotrioxide.—Polonium metal reacts immediately with

[6] Archer, *Analyst*, 1956, **81**, 181.
[7] Bagnall, D'Eye, and Freeman, *J.*, 1956, 3385.
[8] Guillot and Haissinsky, *Compt. rend.*, 1934, **198**, 1911.
[9] Haissinsky and Guillot, *J. Phys. Radium*, 1934, **5**, 419.

fuming sulphuric or concentrated selenic acids, or with the corresponding trioxides, forming extremely unstable dark red solids which are probably $PoSO_3$ and $PoSeO_3$ respectively, analogous to the corresponding reactions of elementary tellurium or selenium. Both compounds decompose within a few minutes to black solids (probably PoO) which are rapidly converted into the quadrivalent sulphate or selenate in the presence of excess of acid or acid trioxide. The sulphur compound is soluble in concentrated sulphuric acid,



giving a red solution and gives a pink solution in water which may contain bivalent polonium; both solutions oxidise rapidly on standing. The selenium compound is insoluble in excess of selenic acid.

Experimental

All the experimental work was carried out in dry-boxes in order to minimise the hazards associated with the high levels of α-activity.

Analysis.—The principal difficulty in the analysis of sub-milligram amounts of these compounds lies in the removal of the excess of sulphuric or selenic acid from the preparation. For example, one curie of polonium as the disulphate contains only 67 μg. of combined sulphur, whereas 1 ml. of 2N-sulphuric acid, used for some preparations of this compound, contains 32 mg. of combined sulphur; in order to obtain a realistic analysis it was therefore necessary to ensure that less than 10^{-4} ml. of the acid used in the preparation remained with the solid. Washing the solid with alcohol or acetone gave unsatisfactory results, but the sulphates and selenate were stable to above 400° in air or nitrogen, so that the excess of acid could be largely removed by heating to 380° for 10 min. (sulphates) or 30 min. (selenate). Heating under a vacuum gave rather erratic results, possibly owing to decomposition. Neither the sulphates nor the selenate is volatile and the losses at 380° in 30 min. were less than 0·01%, as determined from the polonium collected on a cooled plate above the specimen.

The analytical method recently described by Archer [5] for the micro-determination of sulphur was found to be applicable with equal precision to the determination of selenate. The method involves the reduction of the sulphate to hydrogen sulphide by a mixture of hypophosphorous, hydriodic, and hydrochloric acids; the hydrogen sulphide is collected in an aqueous sodium hydroxide–acetone trap and is estimated by titration with N/1000-mercuric acetate, dithizone being used as indicator. Experiment showed that the method was reproducible to about 1% in the range 16—128 μg. of combined sulphur or its selenium equivalent. Tellurium and polonium compounds were reduced to the metal under these conditions, and since it would be difficult to estimate the polonium as a suspension in the reducing mixture, and since the α-bombardment from polonium produces a powerful oxidising effect on the reducing agent, the following separation was adopted.

The polonium sulphate or selenate (0·25—2 curies of ^{210}Po) in a slurry of the appropriate acid (1 ml.) was filtered by centrifugation through a 1-cm. No. 4 filter pad mounted in a 10-ml. centrifuge tube. The solid on the filter, after being dried at 380°, was dissolved in 4N-hydrochloric acid (2 × 0·25 ml.), and the solution centrifuged after each addition. The filtrate was added to ammonia solution (0·25 ml.; *d* 0·880) in a second filter-stick, and the precipitated polonium " hydroxide " was separated by centrifugation and washed with redistilled water (2 × 0·1 ml.); the combined filtrates were analysed for sulphate or selenate and the polonium " hydroxide " was dissolved in 4N-hydrochloric acid, the volume made up to 10 ml., and the polonium content determined by α-counting. This separation is almost quantitative; less than 0·5% of the sulphate or selenate appeared in the polonium solution and only 0·2% of the polonium was found in the ammoniacal sulphate or selenate solution. Less than 0·05% of the polonium was adsorbed on the filter-pads.

This analytical procedure requires either sulphur(or selenium)-free reagents or a knowledge of their sulphur or selenium content. All the reagents used, even when prepared by the methods used for work with dithizone, contained detectable traces of sulphur, and hence, for simplicity, the total reagent blank was determined by carrying out the above sequence of operations in the absence of polonium and estimating the sulphur content of the final ammoniacal solution. The results were sensibly constant for each of the pairs of filter-sticks used, but the blank represented a large fraction of the total sulphate or selenate found; some results obtained with one pair of filter-sticks are tabulated.

Reagent blank = 1·9 × 10^{-7} g.-mol. of sulphate.

Compound	^{210}Po μg.	^{210}Po (g.-atoms × 10^6)	SO_3 (moles × 10^6): found	corrected for blank	SO_3 (g.-mol.)/Po (g.-atoms)
$2PoO_2,SO_3$	190	0·907	0·640	0·450	0·497
	143	0·683	0·525	0·335	0·490
$Po(SO_4)_2$	161	0·768	1·710	1·52	1·98
	52·7	0·251	0·710	0·52	2·07

Solubility Determinations.—The solubility data were obtained by keeping polonium tetrachloride or " hydroxide " in contact with acid of known concentration; equilibrium was attained after 3 days. The aqueous phase cannot be sampled directly for the polonium content since it contains small, and, owing to the radiolysis, extremely mobile particles of the polonium compound. These can be removed by centrifugation through a sintered-glass disc, but the radiation attack on the glass leads to the disintegration of the disc after a few centrifugations. An alternative procedure, which gave results identical with those obtained by centrifugal filtration, involved coating the inside of a small centrifuge tube with a thin film of Vaseline; the suspension was placed in the greased tube and centrifuged for a few minutes so that the small crystals stuck to the grease. The polonium was easily recovered by washing with dilute hydrochloric acid. All the determinations were carried out in quadruplicate.

X-Ray Powder Photography.—In order to protect them against accidental breakage, the capillaries were coated with a thin film of a plastic solution consisting of 1 part of " Bostikote 9956 " diluted with 3 parts of " Bostikote " thinner. The transparent film did not affect the *X*-ray powder photographs.

The authors thank Mr. H. A. C. McKay for many helpful discussions concerning the solubility data.

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879. *Cytidine Diphosphate Ribitol from* Lactobacillus arabinosus.

By J. Baddiley, J. G. Buchanan, B. Carss, and A. P. Mathias.

Short acid hydrolysis of a nucleotide from *Lactobacillus arabinosus* gives cytidine-5′ phosphate, ribitol 1-phosphate, and smaller amounts of other substances. Ribitol 1-phosphate is also formed by enzymic hydrolysis of the nucleotide. It was identified by comparison with an authentic sample, enzymic dephosphorylation to ribitol, acid hydrolysis, and oxidation with periodate.

When heated with dilute aqueous ammonia the nucleotide gives cytidine-5′ phosphate and ribitol 1 : 2-(hydrogen phosphate), the latter being identified by comparison with authentic material and by its behaviour on acid hydrolysis. This and other evidence indicates the structure (I) for the nucleotide.

The behaviour of ribitol and its 1-phosphate towards acids is discussed. A specific method for distinguishing ribitol from other pentitols on a microgram scale has been developed.*

We described earlier the presence in *Lactobacillus arabinosus* of two new cytosine nucleotides.[1] After purification,[2] one was shown to be cytidine diphosphate glycerol (CDP-glycerol).[3] In this paper it is shown that the other cytidine nucleotide from the micro-organism is P^1-cytidine-5′ P^2-ribitol-1 pyrophosphate (I), for which we suggest the name cytidine diphosphate ribitol (CDP-ribitol).†

The nucleotide (previously called CPX) is eluted from a Dowex-2 (formate) column just before CDP-glycerol and is usually present in somewhat larger amounts than the latter in aqueous-alcoholic extracts of *L. arabinosus*. It contains two phosphate groups per cytidine residue and, like CDP-glycerol, it has a higher R_P on paper chromatography in *n*-propyl alcohol–ammonia than cytidine-5′ phosphate or cytidine-5′ pyrophosphate.[2] This suggests the presence of a substituent on one of the phosphate groups. As only a few milligrams of the nucleotide have been isolated it was not possible to perform elementary analyses and all work was carried out on material eluted from paper chromatograms.

No acidic or basic group other than those associated with a cytidine diphosphate structure was detected in this nucleotide. Its R_P in the above solvent mixture was slightly lower than that of CDP-glycerol, which suggests that the residue attached to one of the phosphate groups is more hydrophilic than the glycerol residue and so may contain more hydroxyl groups.

Like CDP-glycerol, this nucleotide gives a rapid colour reaction on paper when sprayed with periodate followed by Schiff's reagent.[4] The initial reddish-blue colour intensifies and deepens in shade during several hours. Such behaviour has been attributed to the presence of both nucleoside and acyclic 1 : 2-glycol structures in such a molecule.[3]

When the nucleotide was hydrolysed with N-hydrochloric acid at 100° for 15 minutes and then examined by paper chromatography the only product which absorbed ultraviolet light was cytidine-5′ phosphate whose identification has been described previously.[1] When the paper was sprayed with reagents for the detection of phosphates [5] the main additional non-absorbing product was an organic phosphate which, like the original nucleotide, gave a rapid reaction in the periodate–Schiff test and consequently was probably an acyclic polyhydroxy-phosphate : some inorganic phosphate and small amounts of two slightly faster-moving phosphates were also detected. One of the last two gave a rapid reaction in the periodate–Schiff test, and the other gave a yellow colour which slowly changed to

* A preliminary account of this work has been published (Baddiley, Buchanan, Carss, and Mathias, *Biochim. Biophys. Acta*, 1956, **21**, 191.

† The nomenclature of compounds of this type is discussed briefly in ref. 3.

[1] Baddiley and Mathias, *J.*, 1954, 2723.

[2] Baddiley, Buchanan, Carss, Mathias, and Sanderson, *Biochem. J.*, in the press.

[3] Baddiley, Buchanan, Mathias, and Sanderson, *J.*, 1956, 4186.

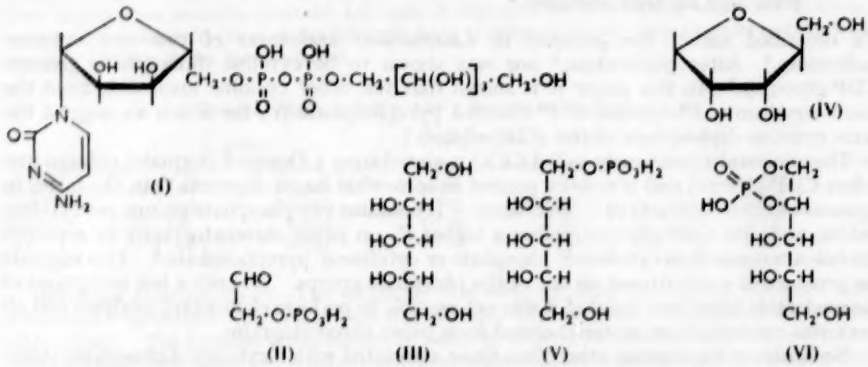
[4] Buchanan, Dekker, and Long, *J.*, 1950, 3162; Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.

[5] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.

grey-green. These are possibly isomers arising through acid-catalysed phosphate migration (cf. the formation of a trace of β-glycerophosphate during the hydrolysis of CDP-glycerol).

The presence of a hydroxyl group in proximity to a phosphate group was suggested by the behaviour of the nucleotide towards ammonia at 100°. After 30 minutes hydrolysis was complete, the products being cytidine-5′ phosphate and a phosphate with a relatively high R_P value in basic solvents. The latter product was recognised as a cyclic phosphate containing a 5-membered ring from its behaviour on chromatography before and after acid hydrolysis. It was readily converted by dilute acids into the same mixture of products as was obtained by the action of acids on the original nucleotide. A 6-membered cyclic phosphate would be stable under such conditions.[6]

The behaviour of the nucleotide towards acids, and especially towards ammonia, is typical of a pyrophosphoric ester which bears a hydroxyl group on a carbon atom adjacent to that bearing the pyrophosphate residue. Several nucleotide coenzymes possess this structural feature and all yield cyclic phosphates on treatment with ammonia.[3, 7, 8]



In the reactions described so far the nucleotide shows some similarity to CDP-glycerol. The main differences are (1) the formation under acid conditions of inorganic orthophosphate and the two unidentified substances, and (2) the greater ease with which a cyclic phosphate is formed in ammonia. The relative ease of cyclic phosphate formation from pyrophosphates will be governed largely by steric factors. In uridine diphosphate glucose,[7] which is a derivative of α-glucose 1-pyrophosphate, and in flavin adenine dinucleotide,[8] where the pyrophosphate group is attached to the terminal position of an acyclic ribityl residue, the adjacent hydroxyl groups are in a sterically favourable position for cyclic phosphate formation. Consequently, these coenzymes are very unstable in ammonia, giving 5-membered cyclic phosphates. In coenzyme A only a 6-membered cyclic phosphate can be formed and so the pyrophosphate linkage in this nucleotide is fairly stable towards alkali.[9] In CDP-glycerol the relative difficulty experienced in forming a cyclic phosphate with ammonia was attributed to the adoption in the glycerol residue of a preferred *trans*-conformation of hydroxyl groups. It is probable that as the length of a polyol 1-phosphate chain increases then the preferred conformation of the hydroxyl group at position 2 will approach the *cis*-relation with respect to the phosphate at position 1. This would facilitate cyclic phosphate formation and hence explain the observed difference in stability of flavin adenine dinucleotide and CDP-glycerol. The conductivity of boric acid solution in the presence of polyols increases very considerably as the length of the polyol chain is increased.

[6] Baddiley and Thain, *J.*, 1951, **3421**; Baddiley, Buchanan, and Szabó, *J.*, **1954, 3826**.
[7] Paladini and Leloir, *Biochem. J.*, 1952, **51**, 426.
[8] Forrest and Todd, *J.*, 1950, 3295.
[9] Baddiley and Thain, *J.*, 1952, 3782.

This is due to the formation of cyclic boric esters, and it has been observed [10] that ethylene glycol and glycerol show only very small effects compared with pentitols and hexitols.

The above considerations suggest that the cytidine nucleotide from *L. arabinosus* is a derivative of a polyol pyrophosphate and that the polyol chain should be larger than that of glycerol. These conclusions are confirmed by the observation that the cyclic phosphate obtained from the nucleotide gives a positive reaction for an acyclic glycol in the periodate–Schiff test. It follows that the polyol must contain at least one 1 : 2-glycol system or its equivalent, in addition to that involved in cyclic phosphate formation. The simplest structure consistent with these observations would be a pyrophosphate formed from cytidine-5′ phosphate and a tetritol phosphate.

The unfractionated phosphatases of *Crotalus atrox* venom hydrolysed the nucleotide readily. The products were cytidine, inorganic phosphate, and an organic phosphate which was indistinguishable from that obtained as a major product of mild acid hydrolysis. This is consistent with a P^1-cytidine-5′ P^2-polyol pyrophosphate structure, as the venom is known to exhibit pyrophosphatase and nucleoside-5′ phosphatase activity.

The organic phosphate produced by enzymic hydrolysis of the nucleotide was eluted from a paper chromatogram and oxidised with periodate. When the products were examined by paper chromatography glycollaldehyde phosphate (II) was detected and identified by comparison with an authentic sample. This indicates that the grouping $H_2O_3P{\cdot}O{\cdot}CH_2{\cdot}CH(OH){\cdot}CH(OH)-$ is present in the hydrolysis product, and that the nucleotide must be a P^1-cytidine-5′ P^2-polyol-1 pyrophosphate.

Further enzymic hydrolysis of the organic phosphate by a mixed phosphatase preparation (Polidase-S) gave inorganic phosphate and a polyol. The polyol was indistinguishable on paper chromatography from authentic ribitol (adonitol) (III), but the differences in R_P values of ribitol and the other two pentitols (xylitol and arabitol) were small (cf. Table).

A more satisfactory identification of ribitol as a product of enzymic hydrolysis of the nucleotide was highly desirable, particularly in view of the complex nature of the acid hydrolysis products. The liberation of inorganic phosphate under relatively mild conditions was somewhat unexpected for a compound of the type shown in formula (I). Cytidine-5′ phosphate and α-glycerophosphate were not hydrolysed under these conditions. This had led us at first to suspect the presence of a centre of unsaturation (double bond or carbonyl group) in the polyol residue. However, no such grouping could be detected, and a more detailed study of the acid hydrolysis of the polyol 1-phosphate was undertaken.

With N-hydrochloric acid at 100° for 1 hour the phosphate was partially hydrolysed to give inorganic phosphate, small amounts of the compound which shows a yellow colour reaction in the periodate–Schiff test, and the other presumably isomeric phosphate, and a new phosphorus-free compound with an R_P higher than that of ribitol. The new compound reacted slowly in the periodate–Schiff test, giving a blue-violet colour. This is consistent with a cyclic structure (cf. nucleosides and other glycosides) and it is probable that an anhydroribitol had been formed. The most likely structure for this product is 1 : 4-anhydroribitol (IV). 1 : 4-Anhydroxylitol has been prepared by acid-catalysed dehydration of xylitol under anhydrous conditions,[11] and it appears that in the hexitols too furan rings are more readily formed than are pyrans.

The ready liberation of inorganic phosphate from the polyol 1-phosphate is almost certainly related in part to the simultaneous formation of an anhydro-compound. The mechanism of this hydrolysis and the structure of the anhydroribitol are under investigation but in the meantime use has been made of these reactions for the full identification of the polyol.

It was found that conversion of ribitol itself into this anhydro-compound in 2N-hydrochloric acid at 100° was substantial in 3 hours (as determined by paper chromatography) and complete in 24 hours. The polyol obtained by enzymic dephosphorylation of the nucleotide behaved in exactly the same way as did authentic ribitol under these conditions and it is concluded that the two compounds are identical. Xylitol was unaffected by 2N-hydrochloric acid at 100° after 24 hours, and arabitol was only very slightly affected.

[10] Böeseken and Furnée, *Rec. Trav. chim.*, 1940, **59**, 97.
[11] Carson and Maclay, *J. Amer. Chem. Soc.*, 1945, **67**, 1808.

The reason for the relative ease with which ribitol is converted into an anhydro-compound, as compared with the other pentitols, is not clear, but here again the adoption of preferred conformations is probably a driving factor. This test is the only one known whereby ribitol can be easily distinguished from other pentitols on a microgram scale.

The formation of anhydroribitol during acid-treatment of ribitol or its 1-phosphate probably occurs by different mechanisms in the two cases. The phosphate reacts much more rapidly under standard conditions than does the polyol itself. Consequently, it is unlikely that hydrolysis to ribitol and inorganic phosphate represents the first stage in this reaction. This is supported by our failure to detect even traces of free ribitol during the hydrolysis of its phosphate.

Confirmation of the structure of the ribitol 1-phosphate from the nucleotide was obtained by comparison with synthetic L-ribitol 1-phosphate (V) (obtained by reduction of D-ribose 5-phosphate with sodium borohydride). The substances were indistinguishable on paper and gave indistinguishable hydrolysis products in identical relative amounts when treated with acid for varying times. Synthetic ribitol phosphate was converted into its 1 : 2-(hydrogen phosphate) (VI) by trifluoroacetic anhydride. This product was indistinguishable on paper chromatography and electrophoresis from that obtained by the action of ammonia on CDP-ribitol.

It has not been possible, with the quantities of CDP-ribitol available, to determine the configuration of the ribitol phosphate residue. It is interesting that if this is D-ribitol 5-phosphate (L-ribitol 1-phosphate) it could be related biochemically to either D-ribose 5-phosphate or D-ribulose 5-phosphate, whereas if it is D-ribitol 1-phosphate (L-ribitol 5-phosphate) it may be related to D-ribose 1-phosphate or D-ribulose 1-phosphate. As most of these pentose phosphates occur naturally it is not possible to predict the configuration of CDP-ribitol.

Although ribitol has been detected in various plants, little is known about its metabolism. It might be predicted on general grounds that CDP-ribitol would be involved in enzymic transformations concerning ribitol 1-phosphate. However, neither this nor any other pentitol phosphate has been detected hitherto in living cells. On the other hand, D-mannitol 1-phosphate has been shown recently to be formed by reduction of fructose 6-phosphate in the presence of enzymes from various bacteria.[12] Moreover, we have isolated D-mannitol 1-phosphate in substantial amounts from *L. arabinosus*.[2] The existence of related metabolic processes involving ribitol phosphates must now be considered.

Experimental

The almost pure nucleotide was isolated from a 100 l. batch of bacterial culture by chromatography on Dowex-2 resin, adsorption on charcoal, and elution with ammonia. Details are described elsewhere.[2] It was purified further by paper chromatography in solvent system *A*, eluted from the paper, and used as a 2% aqueous solution for the following experiments.

Acid Hydrolysis.—A sample of nucleotide was hydrolysed for 15 min. at 100° with N-hydrochloric acid in a sealed tube. Solvent was removed in a desiccator *in vacuo*, and the hydrolysate was examined by paper chromatography in solvent system *A*. Hydrolysis products were identified whenever possible by comparison with authentic substances on adjacent tracks. Cytidine-5′ phosphate and ribitol 1-phosphate were the main products. Some inorganic phosphate, a little "anhydroribitol," and traces of the unidentified "organic phosphate" were detected in addition to the phosphate which gave a yellow spot with the periodate–Schiff spray reagents.[4] For R_P values see Table.

Hydrolysis with Ammonia.—A sample of nucleotide solution was heated with an equal volume of ammonia (*d* 0·88) in a sealed tube at 100° for 30 min. Hydrolysis was complete, the products being cytidine-5′ phosphate and ribitol 1 : 2-(hydrogen phosphate). The cyclic phosphate was eluted from the paper and a sample was shown to be unchanged after 1 hr. at 100° in ammonia (*d* 0·88). A further sample of cyclic phosphate was dissolved in a little N-hydrochloric acid and heated for 5 min. at 100°. The solution was evaporated to dryness in a desiccator, and the products were examined by paper chromatography in solvent system *A*. No starting material was detected. The components of the mixture were indistinguishable

[12] Wolfi and Kaplan, *J. Biol. Chem.*, 1956, **218**, 849.

from the non-nucleotide products of short acid hydrolysis of CDP-ribitol or of synthetic ribitol 1-phosphate.

Paper electrophoresis at 400 v in 0·05M-ammonium acetate buffer (pH 8) of a sample of the cyclic phosphate produced from the nucleotide by ammoniacal hydrolysis showed its identity with the synthetic material. It moved towards the anode at a velocity just over half that of ribitol-1 phosphate.

Action of Crotalus atrox *Venom.*—A solution of the nucleotide was treated with a 1% solution of the venom (kindly supplied by Dr. D. M. Brown) in a glycine–ammonia buffer (pH 9) for 16 hr. at 37°. The products, identified by chromatography in solvent system *A*, were cytidine, ribitol 1-phosphate, and inorganic phosphate.

Enzymic Dephosphorylation of Ribitol 1-Phosphate.—Ribitol 1-phosphate was obtained by the action of snake venom on CDP-ribitol, paper chromatography of the products, and elution of the appropriate area of the paper with water. Traces of inorganic phosphate were removed as barium phosphate with a slight excess of 0·1N-barium hydroxide, followed by a little Dowex-50 (H^+ form) resin to remove barium ions. The resulting ribitol 1-phosphate solution was mixed with a 1% solution of "Polidase-S" (Schwarz Laboratories) in an ammonium acetate buffer (pH 7) and incubated at 37° for 16 hr. The products were inorganic phosphate and ribitol, the latter being identified from its R_P in solvent systems *A*, *B*, *C*, *D*, *E*, and *H*, and by the action of hot dilute hydrochloric acid (see below).

Action of Acid on Ribitol 1-Phosphate.—Ribitol 1-phosphate obtained from the nucleotide by short acid hydrolysis, followed by chromatography (solvent system *A*) and elution, was treated with N-hydrochloric acid at 100° for 15 min. Solvent was removed *in vacuo* and the products were run on paper in solvent system *A*. The products were the same in kind and relative amount as those resulting from a similar treatment of the nucleotide itself (cytidine-5′ phosphate was, of course, absent), the cyclic phosphate, or authentic ribitol 1-phosphate.

Ribitol (100 μg.) in N-hydrochloric acid (20 μl.) was heated in a sealed tube for 1 hr. at 100°. An equivalent amount of synthetic ribitol 1-phosphate was treated similarly. The solutions were evaporated in a desiccator, and products were examined by paper chromatography in solvent system *A*. Under these conditions a weak spot corresponding to anhydroribitol was seen in the ribitol hydrolysis products, whereas the phosphate gave much more anhydro-compound. It was estimated that the phosphate decomposed about 10 times faster than did the free polyol.

Oxidation with Periodate.—To a solution of ribitol 1-phosphate derived from the nucleotide by treatment with snake venom was added a slight excess of 4% sodium metaperiodate solution. After 3 hr. at room temperature sodium ions were removed with a small amount of Dowex-50 (H^+ form) resin, and the products were run on paper in solvent systems *F* and *G*. The spot corresponding to ribitol 1-phosphate was no longer visible but one which was indistinguishable from glycollaldehyde phosphate was present.

Synthesis of Pentitols.—Ribitol, arabitol, and xylitol were obtained from the corresponding pentoses by reduction with sodium borohydride.[13] The pentitols were characterised by the m. p.s of their penta-*O*-acetyl derivatives. Samples were regenerated therefrom by sodium methoxide in methanol. Sodium ions were removed with an excess of Dowex-50 (H^+ form) resin, and evaporation of solvent yielded crystalline products except in the case of xylitol. These were pure when examined by paper chromatography in solvent systems *A*, *B*, *C*, *D*, *E*, and *H*. None of these solvent systems distinguished satisfactorily between the three pentitols.

Action of Acid on Ribitol, Arabitol, and Xylitol.—1% Solutions in water of each pentitol were treated with 2N-hydrochloric acid in sealed tubes at 100° and samples were withdrawn after 3 hr. and 24 hr. After evaporation of solvent the products were run on paper in solvent system *A* and examined with the periodate–Schiff spray reagents. Arabitol and xylitol were unchanged after 3 hr., but about half of the ribitol had been converted into "anhydroribitol." After 24 hr. ribitol had been completely converted into "anhydroribitol," whereas arabitol and xylitol gave only traces of products. Ribitol obtained from CDP-ribitol by the successive action of snake venom and Polidase-S was indistinguishable in behaviour from authentic ribitol.

L-*Ribitol 1-Phosphate.*—To a solution of D-ribose 5-phosphate (180 mg.) in water (4 ml.) was added sodium borohydride (23 mg.) in water (2 ml.). After 12 hr. at room temperature acetic acid (0·3 ml.) was added, followed by dilute ammonia solution (to pH 8—9). The solution was diluted to 20 ml. and passed through a small Amberlite IRA-400 (acetate form) resin column,

[13] Abdel-Akher, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691.

which was then washed with water. Ribitol phosphate was eluted from the resin with N-ammonium acetate solution (30 ml.). Cations were removed by adding an excess of Dowex-50 (H^+ form) resin, and the eluate was evaporated below 25° with repeated additions of water to remove acetic acid, and finally to dryness. Traces of borate which remained in the product interfered with its chromatography. These were removed by evaporation under reduced pressure with anhydrous methanol (4 × 25 ml.). The ribitol 1-phosphate was isolated as its barium salt from aqueous solution (3 ml.) by the addition of a slight excess of 0·1N-barium hydroxide followed by a small piece of solid carbon dioxide. Some water was removed by evaporation under reduced pressure, traces of barium carbonate by centrifugation, and the *barium salt* was precipitated by addition to the centrifugate of an equal volume of ethanol. It was purified by reprecipitation from water with ethanol, washed with acetone, and dried at 80° *in vacuo* (Found : P, 8·4; Ba, 37·2. $C_5H_{11}O_8BaP$ requires P, 8·4; Ba, 37·4%).

L-*Ribitol* 1 : 2-(*Hydrogen Phosphate*).—The barium salt of ribitol 1-phosphate (35 mg.) in water (1·5 ml.) was passed through a small Dowex-50 (H^+ form) resin column and the eluate was freeze-dried. The residue, after drying (P_2O_5) *in vacuo*, was shaken during 1 hr. with trifluoroacetic anhydride (1 ml.) at room temperature. The mixture was evaporated to dryness *in vacuo* and to the residue was added water (1 ml.) and ammonia (1 ml.; *d* 0·88) with shaking. Paper chromatography of the solution in solvent system *A* and electrophoresis showed that the principal product was the cyclic phosphate.

Paper Chromatography.—Unless otherwise stated, ascending front chromatography was carried out on Whatman No. 4 paper which had been washed with 2N-acetic acid, then water. The following solvent systems were used :

A, *n*-Propyl alcohol–ammonia (*d* 0·88)–water (6 : 3 : 1).
B, Pyridine–ethyl acetate–water (2 : 7 : 1).
C, Pyridine–ethyl acetate–water (organic layer) (1 : 2 : 2).
D, *n*-Butyl alcohol–benzene–pyridine–water (organic layer) (5 : 1 : 3 : 3).
E, *n*-Butyl alcohol–acetic acid–water (organic layer) (4 : 1 : 5).
F, *iso*Butyric acid–ammonia (10 : 6 ml.; 0·5N-ammonia).
G, *tert.*-Butyl alcohol–picric acid–water (80 ml. : 2 g. : 20 ml.).
H, *n*-Butyl alcohol–ethanol–water (organic layer) (4 : 1 : 5).

	R_F in solvents								IO_4^-
	A	B	C	D	E	F *	G *	H	Schiff reaction †
Cytidine	0·61	—	—	—	—	—	—	—	S
Cytidine-5′ phosphate	0·20	—	—	—	—	0·53	—	—	S
CDP-ribitol	0·33	—	—	—	—	0·39	—	—	R
Ribitol 1-phosphate	0·34	—	—	—	—	0·39	0·50	—	R
" Organic phosphate "	0·39	—	—	—	—	—	—	—	R
" Yellow spot "	0·39	—	—	—	—	—	—	—	S
" Anhydroribitol "	0·87	—	—	—	—	—	—	—	S
Ribitol 1 : 2-(hydrogen phosphate)	0·53	—	—	—	—	—	—	—	R
Glycollaldehyde phosphate	—	—	—	—	—	0·33	0·50	—	S
Ribitol	0·76	0·22	0·62	0·36	0·34	—	—	0·34	R
Arabitol	0·76	0·20	0·61	0·36	0·35	—	—	0·33	R
Xylitol	0·74	0·21	0·58	0·33	0·34	—	—	0·33	R

* Descending front chromatography. † S = slow reaction, R = rapid reaction.

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becomes readily available; it was hydrolysed by aqueous-alcoholic alkali to tryptamine-2-

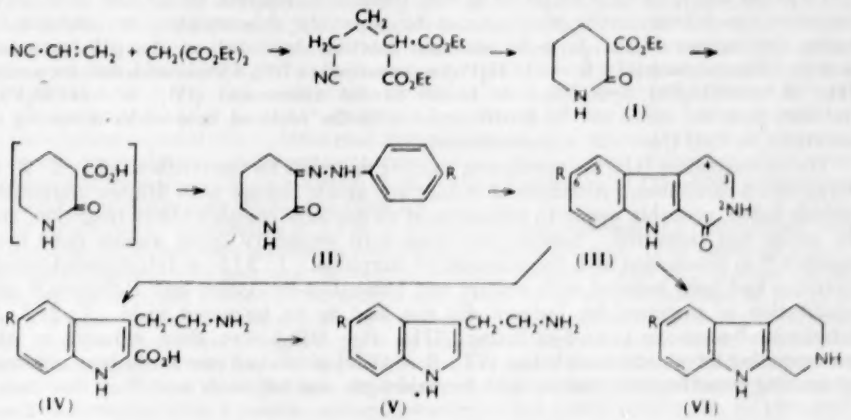
880. *Tryptamines, Carbolines, and Related Compounds. Part II.* A Convenient Synthesis of Tryptamines and β-Carbolines.*

By R. A. Abramovitch and D. Shapiro.

2 : 3-Dioxopiperidine 3-phenylhydrazone was cyclised under acid conditions to 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline. This was hydrolysed to tryptamine-2-carboxylic acid which was decarboxylated to tryptamine. The same reaction sequence with *p*-anisidine afforded a new route to serotonin. 5-Benzyloxytryptamine-2-carboxylic acid could not be decarboxylated to the base. The method also provides a route to the 1 : 2 : 3 : 4-tetrahydro-β-carbolines.

Interest in synthesis of tryptamines has been revived in connection with the synthesis of serotonin (5-hydroxytryptamine) and potential antimetabolites thereof, and a number of methods have been developed. Most of these start from a preformed substituted indole nucleus,[1-4] but preparation of the required precursors is difficult. Two methods [5] do not start from preformed indoles, but again are long or require starting materials which are not readily available. A relatively simple method of preparing tryptamines from tetrahydro-β-carbolines has now been developed.

2 : 3-Dioxopiperidine 3-phenylhydrazone (II; R = H), obtained [6] by a Japp–Klingemann reaction [7] from 2-oxopiperidine-3-carboxylic acid and benzenediazonium chloride, was cyclised to 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline (III; R = H) by polyphosphoric



acid (already used [8] as a catalyst for the Fischer cyclisation). On scales larger than 1 g., however, this reagent caused extensive charring and milder conditions had to be used, *e.g.*, 70% formic acid. The ketocarboline (III; R = H), previously obtained less conveniently by Manske and Robinson [9] and by Keimatsu, Sugasawa, and Kasuya,[10] thus

* The paper on the α-carbolines by Abramovitch, Hey, and Mulley (*J.*, 1954, 4263) is considered to be Part I of this series.

[1] Hamlin and Fischer, *J. Amer. Chem. Soc.*, 1951, **73**, 5007.
[2] Speeter, Heinzelmann, and Weisblat, *ibid.*, p. 5514.
[3] Ek and Witkop, *ibid.*, 1954, **76**, 5579.
[4] (*a*) Asero, Colò, Erspamer, and Vorcellone, *Annalen*, 1952, **576**, 69; (*b*) Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208; Noland and Hartman, *ibid.*, p. 3227.
[5] Harley-Mason and Jackson, *J.*, 1954, 1165; Ewins, *J.*, 1911, **99**, 270; Bernini, *Ann. Chim. appl. Roma*, 1953, **43**, 559; Shaw, *J. Amer. Chem. Soc.*, 1955, **77**, 4319.
[6] Shapiro and Abramovitch, *J. Amer. Chem. Soc.*, 1955, **77**, 6690.
[7] Japp and Klingemann, *Ber.*, 1887, **20**, 2942, 3284.
[8] Kissman, Farnsworth, and Witkop, *J. Amer. Chem. Soc.*, 1952, **74**, 3948.
[9] Manske and Robinson, *J.*, 1927, 240.
[10] Keimatsu, Sugasawa, and Kasuya, *J. Pharm. Soc. Japan*, 1928, **48**, 762; *Chem. Abs.*, 1929, **23**, 834.

for $C_{11}H_{10}ON_2$: C, 70·95; H, 5·4; N, 15·05%). Keimatsu, Sugasawa, and Kasuya [10] give

becomes readily available; it was hydrolysed by aqueous-alcoholic alkali to tryptamine-2-carboxylic acid (IV; R = H), which was decarboxylated to tryptamine (V; R = H) by boiling 5% hydrochloric acid.[10] When absolute-ethanolic potassium hydroxide was used for hydrolysis of the amide, most of the amide was recovered: these or similar conditions may have been used by Nishikawa, Perkin, and Robinson,[11] who were unable to effect the ring opening of 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-oxo-β-carboline by alcoholic potassium hydroxide.

The same sequence of reactions was carried out with diazotised *p*-anisidine in the Japp–Klingemann reaction, to give the methoxyphenylhydrazone (II; R = OMe). The nature of the product obtained in this and similar Japp–Klingemann reactions was found to depend mainly on the pH of the reaction mixture. At pH >7 only a tar was formed, whereas at pH 6—7 a compound was obtained whose properties (instability on attempted purification, formation of a small amount of the phenylhydrazone accompanied by extensive decomposition on quick recrystallisation from water, and transformation into the carboline with ethanolic hydrogen chloride) point to a phenylazo-structure. At pH 3—4 and at 0—5° the required phenylhydrazone was obtained. This could not be cyclised with polyphosphoric acid as tar formation occurred, but 90% formic acid gave the required carboline (III; R = OMe) (previously prepared by Barrett, Perkin, and Robinson by a seven-stage synthesis [12]), which was hydrolysed and decarboxylated as above. Decarboxylation could also be effected with toluene-*p*-sulphonic acid. Since 5-methoxytryptamine has already been demethylated to serotonin [4a] this constitutes a new and convenient synthesis of this compound.

To avoid the final demethylation it was thought of interest to use the benzyloxy-derivative, as 5-benzyloxytryptamine can be smoothly debenzylated to serotonin.[1-3] Again, the success of the Japp–Klingemann reaction depended on the pH (optimum *ca.* 4·5). The product (II; R = O·CH_2Ph) was cyclised in 70% formic acid, and the amide (III; R = O·CH_2Ph) hydrolysed as before to the amino-acid (IV; R = O·CH_2Ph). The last, however, could not be decarboxylated to the required base under a variety of conditions, so that this route was abandoned.

The oxocarbolines (III) are convenient starting materials for the synthesis of 1 : 2 : 3 : 4-tetrahydro-β-carbolines. Attempts to reduce the amide linkage with lithium aluminium hydride failed, probably owing to formation of an insoluble complex before reduction, and the amide was recovered. Similar difficulties with secondary cyclic amides have been reported [13] in connection with the synthesis of morphine. 1 : 2 : 3 : 4-Tetrahydro-1-oxo-β-carboline had been reduced with sodium and butan-1-ol by Ashley and Robinson,[14] and substitution of propanol for butanol did not lead to an increased yield. 1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxo-β-carboline (III; R = OMe) was thus reduced to the corresponding tetrahydro-β-carboline (VI; R = OMe) which had previously been obtained by treating 5-methoxytryptamine with formaldehyde and sulphuric acid.[15]

Experimental

2 : 3-Dioxopiperidine 3-phenylhydrazone was prepared from diazotised aniline and ethyl 2-oxopiperidine-3-carboxylate [16] as described by Shapiro and Abramovitch.[9] The dried crude product was used directly for the next stage.

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxo*-β-*carboline*.—(i) *By use of polyphosphoric acid.* The phenylhydrazone (1 g.) and polyphosphoric acid (5 c.c.) were slowly heated in an oil bath with stirring. When the internal temperature reached *ca.* 105° the solid dissolved, and the internal temperature rose to 120—125° (bath-temp. 105°) and was kept there for 5 min. The cooled mixture was treated with water; the resulting oil solidified on trituration (0·85 g.; m. p. 183—185° after softening at 174°), was filtered off, washed with water, and recrystallised from very dilute alcohol, giving colourless needles, m. p. 183—185° (Found: C, 71·3; H, 5·5; N, 15·3. Calc.

[11] Nishikawa, Perkin, and Robinson, *J.*, 1924, **125**, 657.
[12] Barrett, Perkin, and Robinson, *J.*, 1929, 2942.
[13] Gates and Tschudi, *J. Amer. Chem. Soc.*, 1956, **78**, 1380.
[14] Ashley and Robinson, *J.*, 1928, 1376.
[15] Späth and Lederer, *Ber.*, 1930, **63**, 2102.
[16] Albertson and Fillman, *J. Amer. Chem. Soc.*, 1949, **71**, 2819.

for $C_{11}H_{10}ON_2$: C, 70·95; H, 5·4; N, 15·05%). Keimatsu, Sugasawa, and Kasuya [10] give m. p. 188—189°. The *picrate* separated from alcohol as orange-yellow plates, m. p. 195—197° (Found: C, 49·5; H, 3·5; N, 16·9. $C_{11}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 49·2; H, 3·2; N, 16·9%).

(ii) *By use of* 70% *formic acid.* The phenylhydrazone (1 g.) was boiled under reflux with 70% formic acid (4 c.c.) for ½ hr., the hot solution was diluted with water, and the oil which separated just brought into solution by the dropwise addition of hot alcohol. The hot solution was seeded and allowed to cool, and the oxocarboline (0·7 g.), m. p. 183—185°, filtered off.

Tryptamine-2-carboxylic Acid.—The following are the optimum conditions found for this ring-opening. The carboline (0·5 g.) was boiled under reflux with 2N-potassium hydroxide in 50% ethanol (10 c.c.) for 5 hr. The solvent was evaporated (5 c.c.), water (5 c.c.) added, and the cooled solution filtered. Acidification with acetic acid gave the amino-acid as rosettes of needles (0·45 g.), m. p. 241—242° (decomp.) (from dilute alcohol) (Found: C, 64·8; H, 5·6. Calc. for $C_{11}H_{12}O_2N_2$: C, 64·7; H, 5·9%). Keimatsu, Sugasawa, and Kasuya [10] give m.p. 257°.

Tryptamine.—Tryptamine-2-carboxylic acid (0·33 g.) was boiled under reflux with 5% aqueous hydrochloric acid (5 c.c.) for 1 hr., then the evolution of carbon dioxide ceased. Making the solution alkaline gave tryptamine (0·2 g.), m. p. 115°. The picrate (from dilute acetone) had m. p. 245—246° (decomp.) (Found: C, 49·6; H, 3·8. Calc. for $C_{10}H_{12}N_2,C_6H_3O_7N_3$: C, 49·4; H, 3·9%).

1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline.*[14]—1 : 2 : 3 : 4-Tetrahydro-β-carboline (0·30 g. from 1 g. of amide) was obtained as colourless plates, m. p. 200—202° (reported,[14] m. p. 204°), giving a picrate which on recrystallisation from alcohol–acetone had m. p. 253° (decomp.).

Action of Diazotised p-*Anisidine on* 2-*Oxopiperidine-3-carboxylic Acid.*—(i) *At* pH 6—7. *p*-Anisidine (2·5 g.) in water (30 c.c.) containing concentrated hydrochloric acid (5·5 c.c.) was diazotised at 0—5° with sodium nitrite (1·8 g.) in water (5 c.c.), and the diazonium solution added at 10—12° to one of ethyl 2-oxopiperidine-3-carboxylate (3·4 g.) in water (40 c.c.) containing potassium hydroxide (1·2 g.), which had been kept overnight at 30°. The stirred solution was brought to pH 6—7 by addition of saturated aqueous sodium acetate, and stirring was continued for 2 hr. The solution became cloudy when the temperature reached 15° and the precipitate (1·6 g.), m. p. 112·5° (decomp.), was filtered off and dried. This is probably the phenylazo-compound, for on attempted recrystallisation from most solvents it decomposed. Two quick recrystallisations from water (charcoal) gave a small amount of the phenylhydrazone (accompanied by extensive decomposition) as pale-yellow needles, m. p. 175—176°, undepressed on admixture with a sample obtained as under (ii).

(ii) *At* pH 3—4. *p*-Anisidine (5 g.) in water (60 c.c.) and concentrated hydrochloric acid (11 c.c.) was diazotised with sodium nitrite (3·6 g.) in water (10 c.c.). The excess of nitrous acid was decomposed with urea, and the solution neutralised below 0° with 10% aqueous sodium carbonate (45 c.c.) and filtered. The filtrate was added to an ice-cold solution of the ester (6·8 g.) in water (80 c.c.) containing potassium hydroxide (2·4 g.), which had been kept overnight at 30°, and the solution was brought to pH 3—4 with glacial acetic acid and stirred at 0—5° for 6 hr. The suspension was kept in the refrigerator overnight, then filtered, and the product washed with water and dried (6·7 g.). A sample, on recrystallisation from water (charcoal), gave 2 : 3-*dioxopiperidine* 3-p-*methoxyphenylhydrazone* as flat yellow needles, m. p. 176—177° (Found: C, 62·1; H, 6·7; N, 18·0. $C_{12}H_{15}O_2N_3$ requires C, 61·8; H, 6·5; N, 18·0%).

Cyclisation of the Phenylazo-derivative.—Dry hydrogen chloride was bubbled through the solid (1 g.) suspended in alcohol (40 c.c.). The solid dissolved and evolution of heat which was not controlled caused the solution to boil. The solution was then evaporated to a small volume and treated with water. The black precipitate (0·4 g.) was recrystallised from alcohol (charcoal), giving 1 : 2 : 3 : 4-tetrahydro-6-methoxy-1-oxo-β-carboline as colourless prisms, m. p. 275—277° (Found: C, 66·95; H, 5·7. Calc. for $C_{12}H_{14}O_2N_2$: C, 66·65; H, 5·6%). Barrett, Perkin, and Robinson [13] give m. p. 280°.

Cyclisation of the p-*Methoxyphenylhydrazone.*—The phenylhydrazone (5 g.) was boiled under reflux with 90% formic acid (20 c.c.) for ½ hr. and diluted with water (40 c.c.). The oxocarboline (3·1 g.), m. p. 271—273°, gave colourless crystals, m. p. 275—277°, on recrystallisation from alcohol.

5-*Methoxytryptamine-2-carboxylic Acid.*—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxo-β-carboline (0·5 g.) was boiled under reflux with potassium hydroxide (1·1 g.) in 60% aqueous ethanol (12 c.c.) for 5 hr. The ethanol was evaporated and water (6 c.c.) added. The filtered cold solution was made just acid with acetic acid, giving *5-methoxytryptamine-2-carboxylic acid* (0·53 g., 98%), m. p. 238—240° (decomp.). Recrystallisation from water containing a little

alcohol (charcoal) gave colourless plates, m. p. 246—248° (decomp.) (Found: C, 61·7; H, 5·8. $C_{13}H_{14}O_3N_2$ requires C, 61·5; H, 6·0%).

5-Methoxytryptamine.—(i) 5-Methoxytryptamine-2-carboxylic acid (2 g.) was boiled under reflux with 5% hydrochloric acid (30 c.c.) for 1 hr. The solid soon dissolved with evolution of carbon dioxide. The cooled solution was made alkaline with 30% aqueous sodium hydroxide, the colourless oil was extracted with ether, and the ether dried ($MgSO_4$) and evaporated, giving 5-methoxytryptamine (1·45 g.), m. p. 120—121°. The picrate (from alcohol) formed deep red flat prisms, m. p. 219° (decomp.) (Found: C, 49·2; H, 4·2; N, 16·3. Calc. for $C_{11}H_{14}ON_2,C_6H_3O_7N_3$: C, 48·7; H, 4·1; N, 16·7%). Wieland *et al.*[17] give m. p. 220° (decomp.).

(ii) The amino-acid (0·5 g.) and toluene-*p*-sulphonic acid (4·2 g.) in water (5 c.c.; 5N-solution) were boiled under reflux for 1 hr. The solution was made alkaline and extracted with ether, giving 5-methoxytryptamine (0·2 g.), m. p. 119—120°.

1 : 2 : 3 : 4-*Tetrahydro-6-methoxy-β-carboline.*—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxo-β-carboline (1 g.) was suspended in boiling dry butanol (25 c.c.) and treated rapidly with pieces of sodium (2·5 g.), vigorous stirring and heating (oil-bath) being maintained (the external temperature should not be allowed to rise too much, otherwise considerable charring occurs). After ½ hr., when all the sodium had dissolved, the mixture was cooled and 90% ethanol (25 c.c.) followed by water (25 c.c.) was added, the mixture was steam-distilled, then cooled, and the product recrystallised from dilute methanol, giving 1 : 2 : 3 : 4-tetrahydro-6-methoxy-β-carboline (0·35 g.) as slightly brown needles, m. p. 221—222° (Späth and Lederer[15] give m. p. 223—224°). The *picrate* (from alcohol) had m. p. 240—241° (decomp.) (Found: C, 50·5; H, 4·3. $C_{12}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 50·1; H, 3·9%).

2 : 3-*Dioxopiperidine* 3-p-*Benzyloxyphenylhydrazone.*—*p*-Benzyloxyaniline[18] (2 g.) was heated with concentrated hydrochloric acid (3 c.c.) in water (20 c.c.) until solution was complete. The solution was stirred, and diazotised at 0° with sodium nitrite (0·9 g.) in water (5 c.c.). After 30 min. the excess of nitrous acid was decomposed with urea, and the solution filtered and added at 0° to one of ethyl 2-oxopiperidine-3-carboxylate (1·7 g.) in water (20 c.c.) containing potassium hydroxide (0·6 g.), which had been kept at 30° overnight. After being stirred for ½ hr. at 0° the suspension was brought to pH 4·5 with saturated aqueous sodium acetate and stirring was continued at 12° for 5 hr. The precipitate was filtered off and the filtrate, whose pH had fallen to *ca.* 2, was brought to pH 4, stirred for another 2 hr., and kept in the refrigerator at 2° overnight. The solid was filtered off, washed with water, and dried. The combined solids (2·08 g.), m. p. 166—170°, were recrystallised from very dilute alcohol, giving the 3-p-*benzyloxyphenylhydrazone* as small pale yellow plates, m. p. 185—186° (Found: C, 70·2; H, 5·8; N, 14·3. $C_{18}H_{19}O_2N_3$ requires C, 69·9; H, 6·2; N, 13·6%).

6-*Benzyloxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxo*-β-*carboline.*—The crude *p*-benzyloxyphenylhydrazone (8 g.) was boiled under reflux with 70% formic acid (30 c.c.) for ½ hr., then diluted with water. The product was triturated with a little cold 90% ethanol and collected, giving the colourless *carboline* (5·2 g.), which on recrystallisation from dilute ethanol gave colourless needles, m. p. 199—201° (Found: C, 73·95; H, 5·1. $C_{18}H_{16}O_2N_2$ requires C, 73·95; H, 5·5%).

5-Benzyloxytryptamine-2-carboxylic Acid.—The foregoing carboline (1 g.) was boiled under reflux for 5 hr. with 60% aqueous-ethanolic potassium hydroxide (2·2 g. in 20 c.c.). Working up as above gave the product (1 g.) which recrystallised from 90% ethanol, giving *5-benzyloxytryptamine-2-carboxylic acid* as colourless flat prisms, m. p. 243—244° (decomp.) (Found: C, 69·7; H, 5·75. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·85%).

The amino-acid (0·5 g.) was boiled under reflux with toluene-*p*-sulphonic acid (0·5 g.). An oil was formed which solidified on ½ hour's boiling. The suspension was diluted with water, cooled, and filtered, and the product (0·7 g.), m. p. 198° (effervescence, decomp.), was recrystallised from very dilute alcohol (charcoal), giving the *amino-acid toluene-p-sulphonate* as small colourless needles, m. p. 197—198° (effervescence) (mixed m. p. with 6-benzyloxy-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline, 165—180°) (Found: C, 62·3; H, 5·4. $C_{18}H_{18}O_3N_2,C_7H_8O_3S$ requires C, 62·2; H, 5·4%).

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[17] Wieland, Konz, and Mittasch, *Annalen*, 1934, **513**, 1.
[18] Boehme, *J. Amer. Chem. Soc.*, 1953, **75**, 2502.

881. *Tryptamines, Carbolines, and Related Compounds. Part III.*[1] 1-*Methyl-* and 1 : N-*Dimethyl-tryptamines.*

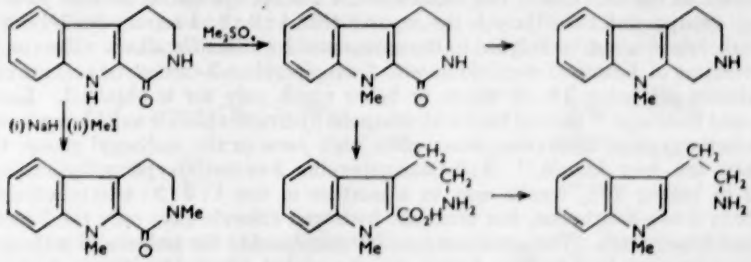
By R. A. Abramovitch.

The scope of the synthesis of tryptamines from 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carbolines has been examined. Substituents in the benzene ring affect the ease of decarboxylation of the tryptamine-2-carboxylic acids, in the order OMe > Me > H > Cl > NO_2 : an explanation is suggested. Tetrahydro-oxocarbolines with dimethyl sulphate give the 9-methyl compounds from which the 1-methyltryptamines can be obtained; the amide group is unreactive but can be methylated by prolonged treatment with sodium hydride followed by methyl iodide, to give the 2 : 9-dimethyl compound in which the amide group now behaves normally, though it is resistant to alkaline hydrolysis. Acid hydrolysis leads to *NN'*-dimethyltryptamine. Cyclisation of 2 : 3-dioxopiperidine 3-*m*-methoxyphenylhydrazone by formic acid gives a mixture of isomers, whereas ethanolic hydrogen chloride gives only the 7-methoxy-compound which, contrary to report, is hydrolysed normally to the amino-acid.

The infrared spectra of some of the intermediates have been examined and are discussed.

The scope of the tryptamine synthesis reported in the preceding paper [1] has been examined in view of divergent experience in the hydrolysis [1,2] and decarboxylation [1] involved, and in methylations [2,3] in this series. In particular, *N*-methyl derivatives have been investigated.

1 : 2 : 3 : 4-Tetrahydro-1-oxo-β-carboline with dimethyl sulphate in aqueous alkali gave, in a few minutes, a high yield of the 9-methyl compound. The position of the methyl group was determined by alkaline hydrolysis to oily 1-methyltryptamine which was identified as its crystalline picrate, which gave no depression of the m. p. when mixed with a specimen [4,5] kindly supplied by Professor Gaddum. The methylcarboline was reduced with sodium and butanol to 1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline, an oil (picrate, m. p. 240°; Groves and Swan [6] give m. p. 242°), whereas 1 : 2 : 3 : 4-tetrahydro-2-methyl-



β-carboline [7] is a solid, m. p. 208—210° (picrate, m. p. 216—217°). For this reduction lithium aluminium hydride failed as in the case of the unmethylated compound, starting material being recovered, also indicating that the unreactive secondary amide group was still present. Finally, whereas both 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline and its 6-methoxy-derivative showed an NH band at 1575 cm.$^{-1}$ (cyclic imides do not show NH

[1] Part II, Abramovitch and Shapiro, preceding paper.
[2] Nishikawa, Perkin, and Robinson, *J.*, 1924, **125**, 658.
[3] King and Stiller, *J.*, 1937, **466**.
[4] Manske, *Canad. J. Res.*, 1931, **5**, 592.
[5] Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703.
[6] Groves and Swan, *J.*, 1952, **650**.
[7] Boekelheide and Ainsworth, *J. Amer. Chem. Soc.*, 1950, **72**, 2132; Witkop and Goodwin, *ibid.*, 1953, **75**, 3376.

bands in this region [8]) the methylated product does not show this band. The *ind-N*-methylation was somewhat unexpected, since an indole-nitrogen atom is not usually methylated under such mild conditions, whereas some amide nitrogen atoms are.[9] Thus, indole is methylated by methyl toluene-*p*-sulphonate by boiling in xylene in 90 hr.[10a] Alternatively, the indole-nitrogen atom can be methylated by forming the sodium salt in liquid ammonia and treating it with methyl iodide.[10b] King and Stiller [3] showed that methylation of methyl 1 : 2-dihydro-1-oxo-β-carboline 3-orthoformate in acetone with methyl sulphate and potassium carbonate for 3 hr. gave methyl 1 : 2-dihydro-2 : 9-dimethyl-1-oxo-β-carboline-3-carboxylate, but that, if the potassium salt of the orthoformic ester was treated with methyl iodide or the orthoformic ester itself was treated with diazomethane, methylation took place at the amide-nitrogen atom. In our hands, treatment of 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline in acetone with dimethyl sulphate and potassium carbonate (anhydrous conditions) still gave the 9-methyl compound, even in the presence of an excess of dimethyl sulphate. Diazomethane did not methylate the compound at all. Dimethylation (no NH band in the 3 μ region, amide-CO band at 1650 cm.$^{-1}$) was achieved by forming the disodio-derivative with sodium hydride in toluene and treating this with methyl iodide. On use of shorter reaction times only partial formation of the disodium salt occurred, for on methylation 1 : 2 : 3 : 4-tetrahydro-9-methyl-1-oxo-β-carboline was also obtained. 1 : 2 : 3 : 4-Tetrahydro-2 : 9-dimethyl-1-oxo-β-carboline could now be reduced with lithium aluminium hydride, to give 1 : 2 : 3 : 4-tetrahydro-2 : 9-dimethyl-β-carboline (no bands in the 3 and the 6 μ region). It could not, however, be hydrolysed under alkaline conditions. Acid hydrolysis gave 1-methyl-3-2′-methylaminoethylindole. These methylations thus lay the basis for convenient syntheses of 1-methyl- and 1 : *N*-dimethyltryptamine.

Preliminary experiments showed that the cyclic amide group was unreactive even towards phosphorus pentachloride, both in 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline and its 9-methyl derivative, starting material being recovered under the conditions under which 1 : 2-dihydro-1-oxo-β-carboline-3-carboxylic acid [3] and 1 : 2-dihydro-9-methyl-1-oxo-β-carboline [11] and its 6-methoxy-derivative [12] were converted into the 1-chloro-compound. [In connection with the unreactivity of this amide group, it is interesting that 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline condenses readily with methyl anthranilate in the presence of phosphorus trichloride [13] to give rutaecarpine.[14]]

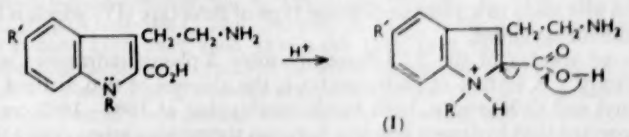
Extension of the synthesis to 6-methoxytryptamine is of two-fold interest: first, there is the question of the direction of ring-closure in the Fischer cyclisation *ortho* or *para* to the methoxyl group; and then there is the report [2] that 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-oxo-β-carboline [15] is not hydrolysed to the amino-acid by ethanolic alkali. The conditions for the reaction of diazotised *m*-anisidine with 2-oxopiperidine-3-carboxylic acid are critical, the optimum pH being 3·6—4, above or below which only tar is obtained. Kermack, Perkin, and Robinson [16] showed that with ethanolic hydrogen chloride indole-ring formation of a *m*-methoxyphenylhydrazone takes place only *para* to the methoxyl group, though exceptions are now known.[17] 2 : 3-Dioxopiperidine 3-*m*-methoxyphenylhydrazone was cyclised in boiling 70% formic acid to a mixture of the 1 : 2 : 3 : 4-tetrahydro-5- and -7-methoxy-1-oxo-β-carboline, but ethanolic hydrogen chloride gave only the 7-methoxy-compound (poor yield). The latter was readily hydrolysed to the amino-acid with aqueous-ethanolic potassium hydroxide and then decarboxylated smoothly with 5% hydrochloric acid to 6-methoxytryptamine.[18] Again, in contrast to the results of Nishikawa *et al.*,[2]

[8] Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1954, p. 176.
[9] Abramovitch, Hey, and Long, unpublished results.
[10] (*a*) Shirley and Roussel, *J. Amer. Chem. Soc.*, 1953, **75**, 377; (*b*) Potts and Saxton, *J.*, 1954, 2641; Anet, Chakravarti, Robinson, and Schlittler, *J.*, 1954, 1254.
[11] Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1884.
[12] Kermack and Tebrich, *J.*, 1940, 314.
[13] Asahina, Manske, and Robinson, *J.*, 1927, 1708.
[14] Cf. Asahina and Ohta, *J. Pharm. Soc. Japan*, 1928, **48**, 313.
[15] Manske and Robinson, *J.*, 1927, 240.
[16] Kermack, Perkin, and Robinson, *J.*, 1921, **119**, 1602; see also Mentzer, *Compt. rend.*, 1946, **222**, 1176; Borsche, *Annalen*, 1908, **359**, 49.
[17] Koelsch, *J. Org. Chem.*, 1943, **8**, 295; Schofield and Theobald, *J.*, 1949, 796.
[18] Akabori and Saito, *Ber.*, 1930, **63**, 2245.

1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-oxo-β-carboline was methylated with dimethyl sulphate and aqueous alkali to a product which is assumed to be the 9-methyl derivative by analogy with the results reported above.

2 : 3-Dioxopiperidine 3-*p*-nitrophenylhydrazone was readily formed (also a *p*-chlorophenylhydrazone), in agreement with the effect of electron-attractive substituents in the ring on the reactivity of the diazonium cation.[19] This phenylhydrazone was not cyclised by boiling formic or acetic acid, but polyphosphoric acid gave a good yield of 1 : 2 : 3 : 4-tetrahydro-6-nitro-1-oxo-β-carboline. Attempts to decarboxylate 5-nitrotryptamine-2-carboxylic acid failed. In view of the high melting point of both the carboline and the amino-acid, experiments on thermal decarboxylations were carried out with tryptamine-2-carboxylic acid. No product could be obtained with copper or its salts and quinoline;[20] when heated in resorcinol at 235°[21] or in glycerol at 210°,[22] the compound cyclised, to give 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline (similar results were obtained with 5-chlorotryptamine-2-carboxylic acid) without decarboxylation. *ind-N*-Methylation of the imide followed by alkaline hydrolysis gave 1-methyl-5-nitrotryptamine-2-carboxylic acid, and though this was not affected by the usual mild acid treatment much more vigorous and prolonged (10 days) treatment gave a small amount of 1-methyl-5-nitrotryptamine. Similar results were obtained with 5-chlorotryptamine-2-carboxylic acid. This was decarboxylated under vigorous acid conditions in 18 hr., whereas 5-chloro-1-methyltryptamine-2-carboxylic acid only required 2 hr. under the same conditions to give 5-chloro-1-methyltryptamine. Reduction of 6-chloro-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline with sodium and *n*-butyl alcohol resulted in elimination of the halogen and formation of 1 : 2 : 3 : 4-tetrahydro-β-carboline. The synthesis of 7-methyltryptamine was unexceptional and the decarboxylation stage was somewhat easier than for the unsubstituted compound.

The ease of decarboxylation of the tryptamine-2-carboxylic acids in acid media decreases in the order OMe > Me > H > Cl > NO_2 of substituents in the benzene ring, whereas *ind-N*-methylation facilitates decarboxylation under these conditions. This order is the reverse of that expected for normal decarboxylations, the electron-attractive nitro-group generally greatly favouring the heterolysis of the C–C bond linking the carboxyl group or carboxylic anion.[23] Again, it is difficult to see a *direct* influence of the 5-substituent on $C_{(2)}$ of the indole ring. The order of substituents is, however, that of decreasing electron density at the ring-nitrogen atom and it would, therefore, seem that the first stage in the decarboxylation mechanism is co-ordination of a proton at this nitrogen, thus forming a positive centre which will attract electrons from $C_{(2)}$ and favour the heterolysis :



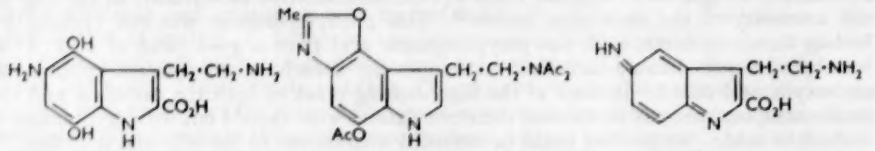
(I)

Only a small amount of the intermediate (I) need be formed. The effect of the indole-*N*-methyl group (R = Me) is in agreement with such a mechanism since it increases the availability of electrons at the nitrogen atom. A 5-benzyloxy-substituent should then favour the ease of decarboxylation and it is hoped to re-examine the decarboxylation of 5-benzyloxytryptamine-2-carboxylic acid later.

Catalytic reduction of 1 : 2 : 3 : 4-tetrahydro-6-nitro-1-oxo-β-carboline gave the 6-amino-compound. Though stannous chloride reduction gave a better yield the product could not be freed from some inorganic material (low analysis for carbon) and the m. p. remained constant on repeated recrystallisations. Its infrared absorption was identical

[19] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell & Sons, London, 1953, p. 298.
[20] Ruggli and Brandt, *Helv. Chim. Acta*, 1944, **27**, 274.
[21] Plieninger, *Chem. Ber.*, 1950, **83**, 268.
[22] Burton and Stoves, *J.*, 1937, 1726.
[23] Brown, *Quart. Rev.*, 1951, **5**, 131.

with that of the product obtained from the catalytic reduction except that the former had, in addition, a very weak band at 952 cm.$^{-1}$. Both compounds gave positive diazo-coupling tests for primary amines, and on hydrolysis by aqueous-ethanolic potassium hydroxide both gave good yields of the same amino-acid (II) which, however, was not the expected



5-aminotryptamine-2-carboxylic acid. This product had an infrared spectrum characteristic [24] of this series of amino-acids (see p. 4599), but in addition, a shoulder at 3571 cm.$^{-1}$ seems to indicate the presence of a hydroxyl group. It is insoluble in organic solvents but soluble in aqueous acids and alkalis, giving reddish-purple solutions (the compound itself is brownish-purple). It contains a high proportion of oxygen, compatible with its being 5-amino-(?4 : 7)-dihydroxytryptamine-2-carboxylic acid (II). Acetylation gives a product whose infrared spectrum (p. 4599) and analysis ($C_{18}H_{13}O_6N_3$) indicate that it may have structure (III). The acetyl determination indicates the presence of 3—4 acetyl groups (oxazoline rings can open on alkaline hydrolysis : [25a] presumably this hydrolysis was incomplete). The presence of phenolic hydroxyl groups in (II) is to this extent confirmed [chelated-ester band at 1715 cm.$^{-1}$ in (III)]. Also, benzoxazoles are known [25b] to give strong bands at 1724—1692 cm.$^{-1}$, where our acetate absorbs. The acetate is insoluble in alkali, so that a band at 1701 cm.$^{-1}$ is not due to a carboxyl group but is attributed to one of the carbonyl groups in the *N*-diacetyl derivative. The possibility that one of the carbonyl groups of an *N*-diacetyl compound behaves more like a normal keto-group was indicated by the fact that 2-*o*-aminobenzoyl-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline gives the Schiff's base rutaecarpine.[14] This possibility is also supported by the observation that 2-acetyl-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline (obtained by acetylation of 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline) shows two strong bands at 1701 and 1672 cm.$^{-1}$, the latter being the normal amide I band in a monosubstituted amide. The indole-NH band for our acetate is very weak, probably because of chelation with the adjacent acetate grouping. Aerial oxidation during the alkaline hydrolysis is not entirely unexpected, since a 5-aminoindole derivative can be considered as a substituted *p*-phenylenediamine. It is possible that oxidation first leads to a quinone di-imine type of structure (IV) which is then hydrated to give the dihydroxyamine.

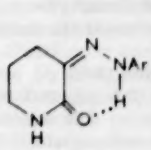
The infrared spectra of the 2 : 3-dioxopiperidine 3-phenylhydrazones were examined during this study. A feature of their spectra is the absence of two distinct bands for the amide-carbonyl and C=N groups, both bands overlapping at 1664—1667 cm.$^{-1}$. It would have been expected that hydrogen bonding between the amide-carbonyl and the hydrazone-NH groups would have lowered the carbonyl absorption in the same way as in vomicine and in *N*-acetyl-4-hydroxyproline.[26] Thus, diacetyl monophenylhydrazone (V) in which hydrogen bonding similarly lowers the ketonic absorption frequency to 1658 cm.$^{-1}$ again shows no distinct band for the C=N grouping, whereas pyruvamide phenylhydrazone (VI) (which is an open-chain analogue of 2 : 3-dioxopiperidine 3-phenylhydrazone) exhibits the C=N stretching band at 1667 cm.$^{-1}$ and the hydrogen-bonded amide I band at 1650 cm.$^{-1}$ as a slightly more intense peak. The absence of evidence for hydrogen bonding in the dioxopiperidine phenylhydrazones might be explained on the basis of a preferred *anti*-structure (VII) for these compounds. Pyruvamide phenylhydrazone (yellow needles,

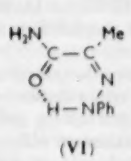
[24] Bellamy, *op. cit.*, p. 202.

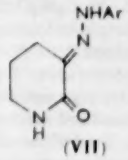
[25] (*a*) Gilman, "Organic Chemistry," Wiley & Sons Ltd., New York, 1953, Vol. IV, p. 808; Meyer and Jacobson, "Lehrbuch der Organischen Chemie," De Gruyter & Co., Berlin, 1920, Band 2, 3 Teil, p. 527; (*b*) Randall, Fuson, Fowler, and Dangl, "Infra-Red Determination of Organic Substances," Van Nostrand Co., New York, 1949, pp. 214—215.

[26] Witkop and Hull, *J. Amer. Chem. Soc.*, 1955, **77**, 6592; Ek and Witkop, *ibid.*, 1954, **76**, 5579.

m. p. 118—119°) is interesting from two other points of view. Gastaldi [27] claims to have obtained this compound as white plates, m. p. 144° (only N analysis given), by the sodium amalgam reduction of the phenylhydrazone of *N*-hydroxypyruvamide, whereas it was prepared in this work from pyruvamide and phenylhydrazine (all the phenylhydrazones with an α-carbonyl group examined so far here are yellow). Again, its infrared spectrum in


(V)


(VI)


(VII)

Nujol mull is interesting because it shows six bands in the 3 μ region : at **3534**, **3484**, **3425**, **3322**, 3247, and **3185** cm.$^{-1}$ (shoulder). These might be explained by the slight solubility of the compound in Nujol leading to some unbonded –NH– stretching bands (the three bands at the higher wave numbers are of lower intensity than the others) owing to the Nujol *solution* of the amide, whereas the other bands are due to the mull proper.

Note added September 27th, 1956.—Since this paper was submitted Hodson and Smith [27a] have shown that the main degradation product ($C_{12}H_{16}N_2$) of folicanthine [27b] is identical with 1-methyl-3-2′-methylaminoethylindole which they prepared from 1-methyltryptamine by formylation followed by reduction with lithium aluminium hydride. They record m.p. 161—173° for the picrate (ours has m.p. 161—169°). The infrared spectrum of our free base is also identical with the one reported by Eiter and Svierak [34] for the folicanthine degradation product, thus confirming the structure deduced by Hodson and Smith for that compound.

Experimental

Infrared spectra were measured on a Grubb-Parsons S4 double-beam spectrometer.

1 : 2 : 3 : 4-*Tetrahydro-9-methyl*-1-*oxo*-β-*carboline*.—1 : 2 : 3 : 4-Tetrahydro-1-oxo-β-carboline (2 g.) in acetone (8 c.c.) and 20% aqueous sodium hydroxide (6 c.c.) was boiled under reflux and treated with dimethyl sulphate (3·2 c.c.). After vigorous stirring and boiling under reflux for 5 min., 20% aqueous sodium hydroxide (4 c.c.) was added, and the solution boiled for a further minute and poured into cold water. The oil which separated solidified (2·1 g.) and after being washed with water the solid was recrystallised from dilute methanol, giving colourless **1 : 2 : 3 : 4-*tetrahydro-9-methyl*-1-*oxo*-β-*carboline***, m. p. 157—158° (Found : C, 71·6; H, 5·9; N, 13·8; *N*-Me, 8·65. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0; N, 14·0; *N*-Me, 7·5%), main infrared bands (in Nujol mull) at **3268**, **3175**, **1647**, **1605**, **1534**, **1453**, 1311, 1292, 741 cm.$^{-1}$.

1-*Methyltryptamine*-2-*carboxylic Acid*.—The crude methylated product (0·75 g.) was boiled under reflux for 6 hr. with a 60% aqueous-ethanolic solution (20 c.c.) of potassium hydroxide (2·2 g.), the ethanol partially evaporated and replaced by water, and the solution filtered and brought to pH 6 with acetic acid. The ***amino-acid*** (0·32 g.), m. p. 243—244°, was filtered off; the mother-liquor deposited a further crop (0·22 g.) overnight. The product recrystallised from very dilute alcohol as colourless plates, m. p. 253—254° (decomp.) (Found : C, 65·8; H, 6·7; N, 12·8. $C_{13}H_{14}O_2N_2$ requires C, 66·1; H, 6·4; N, 12·8%).

1-*Methyltryptamine*.—1-Methyltryptamine-2-carboxylic acid (0·32 g.) was boiled under reflux with 10% hydrochloric acid (5 c.c.) for 1 hr. The solution was made alkaline, the base extracted with ether, and the extract dried ($MgSO_4$) and evaporated, giving an oil (0·27 g.). It was purified as the picrate, m. p. 179—180° (from alcohol containing benzene), undepressed on admixture with the picrate prepared from 1-methyltryptamine kindly supplied by Professor Gaddum (Found : C, 50·4; H, 4·3; N, 16·7. Calc. for $C_{11}H_{14}N_2,C_6H_3O_7N_3$: C, 50·6; H, 4·2; N, 17·4%). Manske [4] gives m. p. 180—181° for 1-methyltryptamine picrate.

1 : 2 : 3 : 4-*Tetrahydro-9-methyl*-β-*carboline*.—The *ind*-*N*-methylamide (1 g.) in dry *n*-butyl alcohol (30 c.c.) was stirred and boiled under reflux (oil-bath at 140°) and treated as quickly as

[27] Gastaldi, *Gazzetta*, 1924, **54**, 212.
[27a] Hodson and Smith, *Chem. and Ind.*, 1956, 740.
[27b] Eiter and Svierak, *Monatsh.*, 1952, **83**, 1453.

possible with pieces of sodium (2·5 g.). Heating and stirring were continued to complete dissolution of the sodium, the cooled solution was treated with 90% ethanol (20 c.c.) and then water (25 c.c.), and the mixture steam-distilled. The residual oil was extracted with ether, and the extract dried ($MgSO_4$). Evaporation of the solvent gave 1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline (0·78 g.) as a brown oil, b. p. 95—120°/0·01 mm., which gave the picrate (from ethanol–acetone) as orange-red needles, m. p. 240° (decomp.) (Found: C, 52·2; H, 4·5. Calc. for $C_{12}H_{14}N_2,C_6H_3O_7N_3$: C, 52·1; H, 4·1%). Groves and Swan[6] give m. p. 242°. The base gave a purple colour in the sulphuric acid-oxidising test,[6] whereas the unmethylated base gives a blue colour.[38].

2 : 3-*Dioxopiperidine* 3-p-*Nitrophenylhydrazone*.—*p*-Nitroaniline (1·52 g.) was dissolved in hot water (30 c.c.) containing concentrated hydrochloric acid (2·5 g.), and the stirred cold suspension diazotised with sodium nitrite (0·9 g.) in water (5 c.c.). The solution was filtered and added at 5—10° to a solution of ethyl 2-oxopiperidine-3-carboxylate (1·7 g.) in water (20 c.c.) containing potassium hydroxide (0·6 g.), which had been kept at 30° overnight, and the suspension stirred at that temperature for 3½ hr. until carbon dioxide was no longer evolved. The product (2·8 g.), m. p. 213—215° (decomp.), was collected, washed with water, and recrystallised from dilute acetic acid, giving the 3-p-*nitrophenylhydrazone* as golden-yellow needles, m. p. 220—221° (decomp.) (Found: C, 53·0; H, 4·9. $C_{11}H_{12}O_3N_4$ requires C, 53·2; H, 4·9%).

1 : 2 : 3 : 4-*Tetrahydro*-6-*nitro*-1-*oxo*-β-*carboline*.—The hydrazone (1 g.) was heated to 110° with polyphosphoric acid (5 c.c.) until complete dissolution had occurred and no more heat was evolved. The solution was poured into ice-water, and the solid (0·9 g.) filtered off, dried, and recrystallised from 90% acetic acid (charcoal), giving the *carboline* as pale yellow needles, m. p. >300°, which became deeper yellow in air (Found: C, 56·8; H, 3·8; N, 18·2. $C_{11}H_9O_3N_3$ requires C, 57·15; H, 3·9; N, 18·2%).

5-*Nitrotryptamine*-2-*carboxylic Acid*.—The oxocarboline (1 g.; crude) was boiled under reflux for 24 hr. with potassium hydroxide (2·2 g.) in 60% aqueous ethanol (20 c.c.). The deep reddish-brown solution was diluted with water (40 c.c.), filtered, and made acid with glacial acetic acid. The canary-yellow precipitate of the *amino-acid* (0·8 g.) did not melt below 300°, could not be recrystallised (sodium salt separates from hot water as orange plates), and was purified by repeated precipitations from the hot alkaline solution (Found: C, 52·6; H, 4·8; N, 16·7. $C_{11}H_{11}O_4N_3$ requires C, 53·0; H, 4·4; N, 16·9%). The usual methods attempted for decarboxylation failed to give the required base.

1 : 2 : 3 : 4-*Tetrahydro*-9-*methyl*-6-*nitro*-1-*oxo*-β-*carboline*.—1 : 2 : 3 : 4-Tetrahydro-6-nitro-1-oxo-β-carboline (1 g.) in acetone (20 c.c.) and aqueous 20% potassium hydroxide (3 c.c.) was stirred and heated under reflux and treated with dimethyl sulphate (1·6 c.c.); the solid went into solution (red colour) and after a few seconds yellow needles separated. The mixture was diluted with water and filtered, and the *product* (0·82 g.), m. p. 291° (decomp.), washed with cold alcohol and recrystallised from 96% acetic acid, giving pale yellow needles, m. p. 297—298° (decomp.) (Found: C, 58·8; H, 4·9; N, 17·6; *N*-Me, 5·35. $C_{12}H_{11}O_3N_3$ requires C, 59·05; H, 4·5; N, 17·1; *N*-Me, 6·1%).

1-*Methyl*-5-*nitrotryptamine*-2-*carboxylic Acid*.—The nitro-oxocarboline (0·75 g.) was hydrolysed as described for the unmethylated product, giving the *amino-acid* (0·75 g.), which was purified by precipitation from hot alkaline solution as pale-yellow needles, m. p. 307° (decomp.; shrinking at 258°), which became orange-brown in a vacuum over phosphoric oxide at 100° (Found: C, 54·4; H, 5·1. $C_{12}H_{13}O_4N_3$ requires C, 54·75; H, 4·9%).

Decarboxylation. The amino-acid (0·5 g.) in 25% hydrochloric acid (10 c.c.) and glacial acetic acid (4 c.c.) was boiled under reflux for 10 days; most of the solid dissolved, to give a deep brown solution which was filtered, cooled, and made alkaline. The oil was extracted repeatedly with ether, dried ($MgSO_4$), and recovered. The residual oil gave a very impure picrate (from 90% ethanol on standing) which, after a number of recrystallisations from 90% ethanol, gave deep red needles of 1-*methyl*-5-*nitrotryptamine picrate*, m. p. 232—233° (Found: C, 15·8; H, 3·8. $C_{11}H_{13}O_2N_3,C_6H_3O_7N_3$ requires C, 45·5; H, 3·6%).

Formation of 6-*Amino*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxo*-β-*carboline*.—(i) *Catalytically*. 1 : 2 : 3 : 4-Tetrahydro-6-nitro-1-oxo-β-carboline (1 g.) was dissolved in hot glacial acetic acid (75 c.c.) and reduced hot with hydrogen in the presence of 5% palladium–charcoal (1 g.). The filtrate was evaporated to dryness *in vacuo*, and the residue was treated with water, filtered off, and recrystallised from dilute ethanol, giving the *amine* (0·5 g.) as tiny plates, m. p. 281—282° (decomp.) after sintering at 270° (Found: C, 65·55; H, 5·4; N, 20·7. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N,

[38] Harvey, Miller, and Robson, *J.*, 1941, 153.

20·9%), main infrared bands (in Nujol) at 3425, 3236, 1675, 1650 sh., 1587, 1558, 1502 sh., 1335, 1302, 1285, 1229, 1125, 775, 722 cm.$^{-1}$.

(ii) *With stannous chloride.* The nitroamide (1 g.) in glacial acetic acid (25 c.c.) containing concentrated hydrochloric acid (2·2 c.c.; *d* 1·19) and stannous chloride (3 g.; dihydrate) was boiled under reflux for 1 hr. The cooled suspension was filtered and the solid complex decomposed with an excess of 20% aqueous sodium hydroxide. The solid (0·7 g.), m. p. 230° (decomp.), recrystallised from dilute ethanol (charcoal) as plates, m. p. 231—233° (decomp.). The carbon analysis (six determinations) was unsatisfactory, and though the m. p. was unchanged after repeated crystallisations it seems probable that it contains some inorganic impurity (Found: C, 62·6; H, 5·25; N, 21·0%).

Hydrolysis of 6-*Amino*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxo*-β-*carboline*.—The amine (1 g.) was hydrolysed as usual with potassium hydroxide (2·2 g.) in 60% aqueous ethanol (20 c.c.) for 5 hr., the purple solution filtered from some insoluble material and evaporated partially, and glacial acetic acid added dropwise. The product (0·62 g.) was filtered, washed with water and alcohol, and dried. It could not be recrystallised from the usual solvents and when dissolved in dilute alkali was not precipitated on careful acidification. It was purified as much as possible by extraction with boiling water, alcohol, and benzene, and dried *in vacuo* at 100°. The 5-*amino*-(?4 : 7)-*dihydroxytryptamine*-2-*carboxylic acid*, m. p. 257—258° (decomp.), was brownish with a violet tinge (Found: C, 52·6; H, 5·5; N, 17·2; O, 20·7. $C_{11}H_{13}O_4N_3$ requires C, 52·6; H, 5·2; N, 16·7; O, 25·5%) and had infrared bands (in Nujol mull) at 3571 sh., 3484 m, 3401 w, 3195 broad, 2667 broad, 1642 (NH_3^+), 1560 s(CO), 1534, 1519 m, 1511 sh., 1493 sh., 1445, 1406, 1383, 1359, 1344, 1302, 1272, 1239, 1223, 1145, 942, 858, 810 cm.$^{-1}$ (abbreviations have the usual meanings). The amino-acid, when boiled with acetic anhydride and 3 drops of glacial acetic acid for 2 hr., gave a low yield of an acetylated *product*, m. p. 204—205°, white plates (from alcohol) (Found: C, 60·2; H, 5·2; Ac, 40·3. $C_{18}H_{19}O_6N_3$ requires C, 60·5; H, 5·3; 3 × Ac, 36·2; 4 × Ac, 48·0%), insoluble in alkalis, having infrared bands (in Nujol mull) at 3425 vw, 1724 s, 1715 s, 1701 s, 1675 m, sh., 1656 m, sh., 1592 w, broad, 1563 w, broad, 1422, 1379, 1348, 1302, 1279, 1248, 1196, 1140, 1095, 1080, 1052, 1038, 1028, 1016, 986, 976, 950, 826 m, 762 (m) cm.$^{-1}$.

2-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxo*-β-*carboline*.—1 : 2 : 3 : 4-Tetrahydro-1-oxo-β-carboline (0·5 g.) was boiled under reflux for 2 hr. with acetic anhydride (5 c.c.) containing glacial acetic acid (5 drops). The mixture was poured into cold water, and the solid recrystallised from alcohol, giving a nearly quantitative yield of 2-*acetyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxo*-β-*carboline* as colourless needles, m. p. 230—231° (Found: C, 68·1; H, 5·2; Ac, 20·4. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; Ac, 18·9%), infrared bands (in Nujol mull) at 3289, 1701, 1672, 1653 sh., 1631, 1582, 1560, 1538 sh., 1486, 1468, 1439, 1397, 1372, 1325, 1299, 1263, 1242, sh., 1235, 1209, 1203 sh., 1183 sh., 1136, 1075, 1045, 1008, 1000, 948, 930, 913, 768, 748, 728, 702, 680 cm.$^{-1}$.

Action of Heat on Tryptamine-2-*carboxylic Acid*.—(i) Tryptamine-2-carboxylic acid (0·5 g.) in glycerol (5 c.c.) was heated under nitrogen at 230° until gas evolution (water vapour) ceased (10 min.). Water was added to the cooled solution, and the precipitated solid was washed with water and dried, giving 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline (0·25 g.), m. p. and mixed m. p. 182—183°.

(ii) A similar result was obtained by fusing the acid with resorcinol at 225° and isolating the product by extracting the phenol with aqueous alkali.

2 : 3-*Dioxopiperidine* 3-p-*Chlorophenylhydrazone*.—This was prepared as in the previous cases from *p*-chloroaniline (1·3 g.) and 2-oxopiperidine-3-carboxylic acid (from 1·7 g. of the ester) at pH 4. The *phenylhydrazone* (1·98 g.) was obtained as yellow prisms, m. p. 216—217° (from ethyl alcohol), insoluble in hot water and only slightly soluble in hot alcohol, but readily soluble in hot dilute alcohol (Found: C, 55·5; H, 5·13. $C_{11}H_{12}ON_3Cl$ requires C, 55·6; H, 5·05%).

6-*Chloro*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxo*-β-*carboline*.—The chlorophenylhydrazone (1 g.) on refluxing with 90% formic acid as described for the other compounds, gave the *carboline* (0·75 g.), m. p. 219—221°, which on recrystallisation from dilute acetic acid (charcoal) gave colourless needles, m. p. 224·5—225·5° (Found: C, 59·4; H, 4·2. $C_{11}H_9ON_2Cl$ requires C, 59·9; H, 4·1%). Its *picrate* (from ethanol) had m. p. 239—240° (Found: C, 45·7; H, 2·6. $C_{11}H_9ON_2Cl,C_6H_3O_7N_3$ requires C, 45·4; H, 2·7%).

5-*Chlorotryptamine*-2-*carboxylic Acid*.—The carboline (1 g.) gave the *amino-acid* (1 g.), m. p. 257—258° (decomp.), which could not be recrystallised but was purified by precipitation from alkaline solution (Found: C, 53·1; H, 5·1. $C_{11}H_{11}O_2N_2Cl,\frac{1}{2}H_2O$ requires C, 53·3; H, 5·25%).

5-Chlorotryptamine.—(i) The amino-acid was unaffected by refluxing 10% hydrochloric acid. (ii) Fusion of the amino-acid with resorcinol at 230° gave 6-chloro-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline, m. p. and mixed m. p. 223—224°, which gave a picrate, m. p. and mixed m. p. 239—240°.

(iii) The amino-acid (3·25 g.) was boiled under reflux with 20% hydrochloric acid (70 c.c.) and glacial acetic acid (20 c.c.) until complete dissolution occurred (18 hr.). The cooled solution, from which the base hydrochloride separated, was made alkaline and extracted with ether, and the ether dried ($MgSO_4$) and evaporated, giving the base as a brown oil (2·12 g.), which was taken up in ether. Dry hydrogen chloride was passed through the solution and the *hydrochloride*, which separated quantitatively, recrystallised from ethanol–ether as plates, m. p. 296—297° (Found: C, 52·2; H, 5·3; N, 11·8. $C_{10}H_{11}N_2Cl,HCl$ requires C, 51·95; H, 5·2; N, 12·1%). The free base gave *5-chlorotryptamine picrate* as orange-red needles, m. p. 253° (decomp.) (from ethanol) (Found: C, 45·6; H, 3·3; N, 17·0. $C_{10}H_{11}N_2Cl,C_6H_3O_7N_3$ requires C, 45·3; H, 3·3; N, 16·5%), depressed to 215—220° on admixture with the picrate of the oxocarboline obtained under (ii).

Attempted Preparation of 6-Chloro-1 : 2 : 3 : 4-tetrahydro-β-carboline.—6-Chloro-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline (1 g.) in boiling *n*-butyl alcohol (25 c.c.) was stirred in an oil-bath at 140° and treated with sodium (2·5 g.). After all the sodium had dissolved, 90% ethanol (25 c.c.) and then water (25 c.c.) were added, the mixture was steam-distilled, and the residue (0·38 g.) was recrystallised from very dilute alcohol, giving 1 : 2 : 3 : 4-tetrahydro-β-carboline, m. p. 206—207° (Found: C, 76·2; H, 6·9. Calc. for $C_{11}H_{12}N_2$: C, 76·8; H, 7·0%); the picrate had m. p. 253—254° (decomp.) (Found: C, 50·9; H, 3·8. Calc. for $C_{11}H_{12}N_2,C_6H_3O_7N_3$: C, 50·9; H, 3·7%); both m. p.s were undepressed on admixture with authentic specimens.

5-Chloro-1-methyltryptamine-2-carboxylic Acid.—The chloro-oxocarboline (3·5 g.) was methylated as in the case of the nitro-compound, giving the *9-methyl* derivative (3·0 g.), m. p. 204—205·5°, which on recrystallisation from dilute ethanol had m. p. 207—207·5° (Found: C, 61·4; H, 8·2. $C_{12}H_{11}ON_2Cl$ requires C, 61·4; H, 8·3%). This (2 g.), on alkaline hydrolysis for 5 hr. as usual, gave *5-chloro-1-methyltryptamine-2-carboxylic acid* (2·1 g.) as plates (from large volume of dilute ethanol), m. p. 249—250° (decomp.) (Found: C, 56·5; H, 5·2. $C_{12}H_{13}O_2N_2Cl$ requires C, 57·0; H, 5·15%).

5-Chloro-1-methyltryptamine.—The amino-acid (0·5 g.) was boiled under reflux with 20% hydrochloric acid (10 c.c.) and acetic acid (5 c.c.) until complete dissolution had taken place (2 hr.). The solution was made alkaline and extracted with ether, and the extract dried ($MgSO_4$) and evaporated, giving the base (0·31 g.) which solidified overnight when a few drops of ether were added. The solid, m. p. 87—89°, was purified and analysed as the *picrate*, m. p. 203—204° (from 90% ethanol) (Found: C, 47·0; H, 3·5. $C_{11}H_{13}N_2Cl,C_6H_3O_7N_3$ requires C, 46·6; H, 3·7%).

7-Methyltryptamine.—Diazotised *o*-toluidine (from 2·14 g. of base) and 2-oxopiperidine-3-carboxylic acid (from 3·4 g. of ester) gave *2 : 3-dioxopiperidine 3-o-methylphenylhydrazone* (3·3 g.) as pale yellow needles, m. p. 138—139°, from dilute alcohol (Found: C, 66·2; H, 7·0. $C_{12}H_{14}ON_2$ requires C, 66·4; H, 6·9%). The phenylhydrazone (1 g.) with 90% acetic acid (5 c.c.) gave *1 : 2 : 3 : 4-tetrahydro-8-methyl-1-oxo-β-carboline* (0·72 g.) which, recrystallised from dilute acetic acid, had m. p. 195—196° (Found: C, 71·8; H, 6·0. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0%), and gave a brown ⟶ olive-green colour in the sulphuric acid–oxidising agent test. Hydrolysis of the amide (2·8 g.) with aqueous-alcoholic potassium hydroxide for 5 hr. gave *7-methyltryptamine-2-carboxylic acid* (2·3 g.), m. p. 248° (decomp.) (from water) (Found: C, 65·6; H, 6·5. $C_{13}H_{14}O_2N_2$ requires C, 66·1; H, 6·4%). This (0·5 g.), with boiling 10% hydrochloric acid, gave 7-methyltryptamine (0·27 g.), whose picrate (from ethanol) had m. p. 231° (decomp.) (Found: C, 50·2; H, 4·1; N, 17·2. Calc. for $C_{11}H_{14}N_2,C_6H_3O_7N_3$: C, 50·6; H, 4·2; N, 17·4%). Gaddum *et al.*[29] give m. p. 236° (decomp.) for 7-methyltryptamine picrate.

2 : 3-Dioxopiperidine 3-m-Methoxyphenylhydrazone.—*m*-Anisidine (2·5 g.) in water (30 c.c.) and concentrated hydrochloric acid (5 c.c.) was diazotised with sodium nitrite (1·4 g.) in water (10 c.c.). The solution was brought to pH 4 with saturated aqueous sodium acetate. A solution of ethyl 2-oxopiperidine-3-carboxylate (3·6 g.) in water (40 c.c.) containing potassium hydroxide (1·2 g.), which had been left at room temperature overnight, was added to the cold diazonium solution and stirring continued, the pH being kept at 3·6—4·0 all the time (in more acid medium decomposition takes place, whereas at a higher pH the phenylazo-compound separates out and decomposes very quickly). At first a small amount of tar separated and then the yellow solid product. The suspension was allowed to reach room temperature after 2 hr.,

[29] Gaddum, Hameed, Hathway, and Stephens, *Quart. J. Expt. Physiol.*, 1955, **40**, 49.

the liquid was decanted off, and the tarry solid residue boiled for a short while with a little alcohol. The orange-yellow solid was filtered from the cold mixture, washed with a little alcohol, and dried, giving the 3-m-*methoxyphenylhydrazone* (1·92 g.), m. p. 209—210° (decomp.). Recrystallisation from dilute alcohol gave orange-red crystals, m. p. 212—213° (decomp.) (Found: C, 61·5; H, 6·4. $C_{18}H_{18}O_2N_3$ requires C, 61·8; H, 6·5%).

Cyclisation of 2 : 3-*Dioxopiperidine* 3-m-*Methoxyphenylhydrazone.*—(i) *By use of* 70% *formic acid.* The hydrazone (0·5 g.) was boiled under reflux for ½ hr. with 70% formic acid (2·5 c.c.), the solution diluted with water, and the dark oil which separated partially solidified. The mother-liquor was decanted off and the residue taken up in boiling alcohol and cooled. 1 : 2 : 3 : 4-*Tetrahydro*-5-*methoxy*-1-*oxo*-β-*carboline* (0·06 g.), m. p. 208—210°, separated and was recrystallised from ethanol as cream-coloured needles, m. p. 212—213° (Found: C, 66·8; H, 5·2. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6%). The alcohol mother-liquor, on being partially evaporated and cooled, gave 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-oxo-β-carboline (0·10 g.), m. p. 192—193° which, on recrystallisation from dilute ethanol, gave colourless prisms, m. p. 199—200° (Found: C, 66·9; H, 5·8%). Barrett, Perkin, and Robinson [20] give m. p. 198° for this compound. A mixture of the above two carbolines melted at 180—185°.

(ii) *By use of alcoholic hydrogen chloride.* The phenylhydrazone (4·6 g.) in alcohol (100 c.c.) was saturated with dry hydrogen chloride, the solution being allowed to get hot. It was then kept at room temperature overnight (stoppered flask) and the solid (0·96 g.) collected and washed with a little cold alcohol. The alcoholic mother-liquor was evaporated to a small bulk and cooled, and the solid obtained (0·6 g.) added to the first lot and recrystallised from dilute ethanol, giving 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-oxo-β-carboline, m. p. 198—200°.

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-9-*methyl*-1-*oxo*-β-*carboline.*—The methoxy-amide (0·9 g.) was methylated with dimethyl sulphate and sodium hydroxide as described above, giving the ind-N-*methyl* derivative (0·91 g.), m. p. 195—196°, which recrystallised from ethanol as clusters of rods, m. p. 202—203° (Found: C, 67·9; H, 6·2. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1%), depressed to 163—165° on admixture with the starting material.

6-*Methoxytryptamine*-2-*carboxylic Acid* (cf. ref. 2).—1 : 2 : 3 : 4-Tetrahydro-7-methoxy-1-oxo-β-carboline (0·35 g.) was boiled under reflux with a 60% aqueous-ethanolic solution (10 c.c.) of potassium hydroxide (1·1 g.) for 5 hr. and worked up as usual, to give the amino-acid (0·35 g.), m. p. 253—254°, which on recrystallisation from very dilute alcohol gave colourless platelets, m. p. 257—258° (decomp.) (Found: C, 61·6; H, 5·9. Calc. for $C_{12}H_{14}O_3N_2$: C, 61·5; H, 6·0%). Nishikawa, Perkin, and Robinson [2] report that this compound darkens at 220° and progressively decomposes from 220—250° without melting. Its main infrared bands (in Nujol mull) were at 3484, 3401, 3175 broad, 2500 broad, 1639, 1577, 1553, 1522, 1433, 1379, 1299, 1285, 808 cm.$^{-1}$.

6-*Methoxytryptamine.*—The amino-acid (0·2 g.) was boiled with 5% hydrochloric acid (2 c.c.) for 10 min., the solution made strongly alkaline and extracted with ether, and the dried ($MgSO_4$) ether evaporated, giving the tryptamine (0·15 g.), m. p. 144—145°. Akabori and Saito [18] give m. p. 142·5—143·5° for 6-methoxytryptamine. The *picrate* separated from ethanol containing a little dioxan as ruby-red prisms, m. p. 221° (decomp.) (Found: C, 48·8; H, 4·15. $C_{11}H_{14}ON_2.C_6H_3O_7N_3$ requires C, 48·7; H, 4·1%). From water containing a few drops of ethanol the picrate separated as violet needles, m. p. 220—221° (decomp.).

Action of Diazomethane on 1 : 2 : 3 : 4-*Tetrahydro*-1-*oxo*-β-*carboline.*—The amide (1 g.) in methyl alcohol (100 c.c.) was treated with diazomethane (5 mols.) in ether and kept at room temperature for 24 hr. Starting material (0·95 g.), m. p. 185—186°, was recovered.

1 : 2 : 3 : 4-*Tetrahydro*-2 : 9-*dimethyl*-1-*oxo*-β-*carboline.*—1 : 2 : 3 : 4-Tetrahydro-1-oxo-β-carboline (1·86 g.) was dissolved in boiling dry toluene (150 c.c.), the cooled solution treated with sodium hydride (0·60 g., excess), and the mixture boiled under reflux for 18 hr. Methyl iodide (6 c.c.) was added to the mixture, which was boiled for another 4 hr., filtered hot, and evaporated *in vacuo*. The residual oil was distilled, giving 1 : 2 : 3 : 4-*tetrahydro*-2 : 9-*dimethyl*-1-*oxo*-β-*carboline* (1·95 g.) as a pale yellow oil, b. p. 150—152°/0·04 mm., m. p. 65—66° (Found: C, 72·4; H, 6·5; *N*-Me, 16·3. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5; *N*-Me, 14·0%), infrared bands (in Nujol mull) at 1653, 1626, 1546, 1504, 1479, 1431, 1406, 1387, 1362, 1323, 1259, 1244, 1082, 747, and 739 cm.$^{-1}$. The *picrate* (from very dilute ethanol) was orange needles, m. p. 113—113·5° (Found: C, 51·45; H, 4·0. $C_{13}H_{14}ON_2.C_6H_3O_7N_3$ requires C, 51·5; H, 3·8%). If the toluene solution of the amide was refluxed with sodium hydride (0·40 g.) for only 6 hr. before treatment with methyl iodide, evaporation of the solvent to a small volume gave first 1 : 2 : 3 : 4-tetrahydro-9-methyl-1-oxo-β-carboline (0·50 g.), m. p. and mixed m. p. 157°. The mother-liquors gave the *NN'*-dimethylamide (0·8 g.) b. p. 136—138°/0·02 mm., m. p. 65—66°.

[20] Barrett, Perkin, and Robinson, *J.*, 1929, 2942.

Hydrolysis of 1 : 2 : 3 : 4-*Tetrahydro*-2 : 9-*dimethyl*-1-*oxo*-β-*carboline*.—(i) Attempts to effect hydrolysis under alkaline conditions as usual or by boiling overnight failed to give any product and starting material was recovered. (ii) The *NN'*-dimethylamide (0·25 g.) was boiled under reflux with 15% hydrochloric acid (15 c.c.) for 24 hr., by which time all the oil had dissolved. The solution was diluted with water (10 c.c.), filtered, and made alkaline, and the oil which separated extracted with ether. The dried ($MgSO_4$) ether extract was evaporated, yielding an oil (0·19 g.), b. p. 190°/18 mm., from which a deep-red picrate was prepared. Recrystallisation from ethanol gave 1-*methyl*-3-2'-*methylaminoethylindole picrate* as deep-red needles, m. p. 168—169° (Found: C, 51·4; H, 4·7. $C_{13}H_{16}N_2,C_6H_3O_7N_3$ requires C, 51·8; H, 4·6%). The free base gives a positive Ehrlich reaction. Its infrared absorption spectrum (liquid film) shows the absence of carbonyl groups, a very weak band at 1667 cm.$^{-1}$ probably being due to an indole ring vibration.

1 : 2 : 3 : 4-*Tetrahydro*-2 : 9-*dimethyl*-β-*carboline*.—The *NN'*-dimethylamide (0·5 g.) in a Soxhlet extractor was boiled with lithium aluminium hydride (0·5 g.) in dry ether (150 c.c.) for 6 hr. The excess of hydride was decomposed with ethyl acetate, and the complex decomposed with water. The water layer was extracted with ether, and the ether layers were combined, dried ($MgSO_4$), and evaporated, giving 1 : 2 : 3 : 4-*tetrahydro*-2 : 9-*dimethyl*-β-*carboline* (0·31 g.) as an oil which solidified and recrystallised from light petroleum (b. p. 60—80°) as colourless rods, m. p. 95·5—96·5° (Found: C, 77·6; H, 7·8. $C_{13}H_{16}N_2$ requires C, 78·0; H, 8·0%). The *picrate* (from ethanol) gives yellow needles, m. p. 210° (from acetone) (Found: C, 53·4; H, 4·2. $C_{13}H_{16}N_2,C_6H_3O_7N_3$ requires C, 53·1; H, 4·4%). The infrared spectrum of the base (liquid film) has no >NH (or −OH) band, and no amide band in the 6 μ region.

Pyruvamide Phenylhydrazone.—Pyruvamide [31] and phenylhydrazine in very dilute alcohol gave the *phenylhydrazone* as yellow needles, m. p. 118—119°, from dilute ethanol (Found: C, 61·5; H, 6·4. $C_9H_{11}ON_3$ requires C, 61·0; H, 6·2%) [Gastaldi [37] gives m. p. 144° for a colourless product claimed to be pyruvamide phenylhydrazone (only N analysis given) prepared by an ambiguous route]. The infrared spectrum (in Nujol mull) had bands at 3534, 3484, 3425, 3322, 3247, 3185 sh., 1667, 1650, 1608, 1572 broad, 1546, 1504, 1471, 1404, 1385, 1311, 1299 sh., 1264, 1235, 1217, 1174, 1163, 1151, 1075, 891, 774, 746, and 694 cm.$^{-1}$.

Diacetyl monophenylhydrazone was prepared by Benary's method [33] from ethyl methyl ketone and ethyl formate, followed by reaction of the product with benzenediazonium chloride and had infrared bands (in Nujol mull) at 3279, 3145, 1658, 1608, 1570, 1550 sh., 1511, 1484, 1466, 1453, 1429, 1377 sh., 1368, 1342, 1304, 1295, 1252, 1242 sh., 1208, 1185, 1176 sh., 1166, 1159, 1152, 1116, 1000, 995, 939, 758, and 697 cm.$^{-1}$.

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[31] Ankers, *J. Biol. Chem.*, 1949, **176**, 1334.
[33] Benary, *Ber.*, 1926, **59**, 2198.

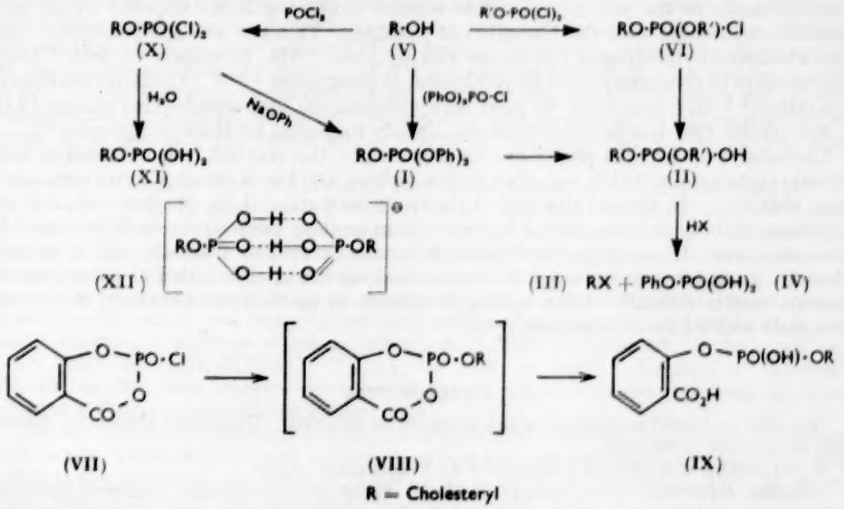
882. *Some Cholesteryl Phosphates.*

By H. A. C. Montgomery, J. H. Turnbull, and W. Wilson.

Cholesteryl diphenyl phosphate with aqueous-alcoholic alkali undergoes both hydrolysis and ethanolysis. The major products are cholesteryl phenyl and cholesteryl ethyl hydrogen phosphates. The structure of these has been established by independent syntheses. The former had been isolated previously when it was believed to be cholesteryl dihydrogen phosphate. The dihydrogen phosphate itself, conveniently prepared from hydrolysis of cholesteryl phosphorodichloridate, forms a stable " half " pyridine salt.

The action of aqueous ethanolic potassium hydroxide on cholesteryl diphenyl phosphate (I) was earlier [1] found to give about 1·75 mol. of phenol, and an acid (m. p. 162°) was isolated. These results have been confirmed but it is now clear that the acid is cholesteryl phenyl hydrogen phosphate (II; R′ = Ph) and not the dihydrogen phosphate as suggested earlier. Two mol. of phenol are not produced even on prolonged reaction, and no phenol is formed from cholesteryl phenyl hydrogen phosphate under these conditions, the anion of the latter being stable to alkali.[cf. 2] The implication that base-catalysed ethanolysis [cf. 3, 4] of cholesteryl diphenyl phosphate was accounting for the liberation of a considerable part of the phenol has now been confirmed by the isolation of cholesteryl ethyl hydrogen phosphate (II; R′ = Et) from the products. Also, phenol was rapidly formed from cholesteryl diphenyl phosphate in cold ***anhydrous*** potassium ethoxide solution.

Solvolysis of cholesteryl phenyl hydrogen phosphate with hydrogen chloride in acetic acid gives 3β-chlorocholest-5-ene (III; X = Cl) and phenyl dihydrogen phosphate (IV), whilst refluxing it with acetic acid yields 3β-acetoxycholest-5-ene (III; X = OAc) and phenyl dihydrogen phosphate, with retention of configuration at $C_{(3)}$ in each case.[cf. 1]



Cholesteryl phenyl hydrogen phosphate was synthesised as follows. Phenyl phosphorodichloridate with cholesterol (V) in 2 : 6-lutidine gave cholesteryl phenyl phosphorochloridate (VI; R′ = Ph). The latter was hydrolysed when refluxed with aqueous

[1] Turnbull and Wilson, *J.*, 1954, 2301.
[2] Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.
[3] Morel, *Compt. rend.*, 1899, **128**, 507.
[4] Rueggerberg and Chernack, *J. Amer. Chem. Soc.*, 1948, **70**, 1802.

*iso*propyl alcohol affording cholesteryl phenyl hydrogen phosphate (II; R′ = Ph). Alternatively the phosphorochloridate (VI; R′ = Ph) was treated with tetrahydropyran-2-ol: the resulting syrup, presumably cholesteryl phenyl tetrahydro-2-pyranyl phosphate, lost dihydropyran when heated, yielding cholesteryl phenyl hydrogen phosphate. This method may be useful for the hydrolysis of other phosphorochloridates of high molecular weight which often yield gelatinous products by direct hydrolysis. Cholesteryl ethyl hydrogen phosphate (II; R′ = Et) was synthesised from ethyl phosphorodichloridate and cholesterol, the intermediate phosphorochloridate (VI; R′ = Et) being indirectly hydrolysed with *tert.*-butyl alcohol.

Most of the known phosphorylation methods [1] were considered unsuitable for the preparation of cholesteryl dihydrogen phosphate. In view of discrepancies in the literature on the properties of this compound an attempt was made to synthesise it by using anhydro-(*o*-carboxyphenyl phosphorochloridate) (VII) as phosphorylating agent. The latter, prepared by refluxing salicylic acid with phosphorus oxychloride, reacted rapidly with cholesterol in 2:6-lutidine yielding cholesteryl *o*-carboxyphenyl hydrogen phosphate (IX), the corresponding anhydride (VIII) probably being an intermediate. Attempts to hydrolyse the phosphate (IX) to cholesteryl dihydrogen phosphate (cf. Chanley and Gindler [5]) failed. It resisted hydrolysis in alkaline or weakly acid aqueous conditions; solvolysis occurred with hydrogen chloride in acetic acid affording 3β-chlorocholest-5-ene.

Hydrolysis of cholesteryl phosphorodichloridate (X) has been claimed to yield cholesteryl dihydrogen phosphate.[6] This has now been confirmed, although the yield of the dihydrogen phosphate is poor, and considerable attention to detail is essential. Cholesteryl phosphorodichloridate, prepared from cholesterol and phosphorus oxychloride in pyridine,[6] was characterised by reaction with sodium phenoxide to give cholesteryl diphenyl phosphate (I). Hydrolysis of the pyridine-free phosphorodichloridate yielded crystalline cholesteryl dihydrogen phosphate (XI). Failure to remove pyridine, as in the procedure of Wagner-Jauregg, Lennartz, and Kothny,[7] invariably yielded the salt $C_5H_5N,2RO{\cdot}PO(OH)_2,H_2O$ which is stable in the presence of dilute mineral acids, but is decomposed by aqueous potassium hydroxide with the liberation of pyridine. This salt was independently made from cholesteryl dihydrogen phosphate and pyridine. The formation of such "half" salts seems to be characteristic of alkyl dihydrogen phosphates.[1, 9, 10] The latter are dimeric in solution,[1, 8] and may tend to yield three-dimensional hydrogen-bonded anions (XII; cf. the similar two-dimensional structures already suggested for these compounds [11]).

Cholesteryl dihydrogen phosphate, as prepared by this method, was obtained as well-defined crystals (m. p. 181°), but other higher-melting and less crystalline forms were sometimes obtained. In view of this and of the ready formation of the pyridine salt, it is not surprising that there is considerable variation in melting points previously recorded for this compound. Cholesteryl dihydrogen phosphate titrated as a dibasic acid in aqueous ethanol. In water, gels were readily formed making the interpretation of potentiometric titration results difficult. With hydrogen chloride in acetic acid cholesteryl dihydrogen phosphate yielded 3β-chlorocholest-5-ene.

Experimental

$[\alpha]_D$ were measured in chloroform unless otherwise specified. Ultraviolet absorption maxima were determined in ethanol.

2 : 6-Lutidine was purified as described by Biddiscombe *et al.*[14]

Alkaline Hydrolysis of Cholesteryl Diphenyl Phosphate.—Cholesteryl diphenyl phosphate (2·4 g.), ethanol (120 c.c.), and 4N-potassium hydroxide (30 c.c.) were refluxed gently for 19 hr. The product, worked up as in Turnbull and Wilson's procedure,[1] yielded *cholesteryl phenyl hydrogen phosphate* (1·0 g.), which formed hygroscopic platelets (from ethyl acetate), m. p. 160°,

[5] Chanley and Gindler, *J. Amer. Chem. Soc.*, 1953, **75**, 4035.
[6] Von Euler, Wolf, and Hellström, *Ber.*, 1929, **62**, 2451.
[7] Wagner-Jauregg, Lennartz, and Kothny, *Ber.*, 1941, **74**, 1513.
[8] Wagner-Jauregg, *J. Org. Chem.*, 1954, **19**, 1483.
[9] Hunter, Roberts, and Kester, *J. Amer. Chem. Soc.*, 1948, **70**, 3244.
[10] Brown, Malkin, and Maliphant, *J.*, 1955, 1584.
[11] Wagner-Jauregg and Wildermuth, *Ber.*, 1944, **77**, 481.

$[\alpha]_D$ −28°, $\lambda_{max.}$ 264 (ε 524) (Found: C, 71·0; H, 10·3; P, 6·0. $C_{33}H_{51}O_4P,H_2O$ requires C, 70·7; H, 9·5; P, 5·5%).

Concentration of the mother-liquors afforded a white solid (700 mg.) and a syrup (400 mg.). Recrystallisation of the solid from benzene–light petroleum then from ethyl acetate yielded cholesteryl ethyl hydrogen phosphate (350 mg.), m. p. 156—157° undepressed by admixture with the synthetic material (below).

In another experiment cholesteryl diphenyl phosphate (49 mg.) was similarly treated with alkali. Liberated phenol (*ca.* 1·6 mol.) was estimated spectrophotometrically. Cholesteryl phenyl hydrogen phosphate was recovered after similar treatment with alkali during 3 days.

Reaction of Cholesteryl Phenyl Hydrogen Phosphate with Hydrogen Chloride.—The phenyl hydrogen phosphate (200 mg.), acetic acid (5 c.c.), and concentrated hydrochloric acid (0·5 c.c.) were warmed (100°) for 10 min. The product was diluted with water and gave 3β-chlorocholest-5-ene (150 mg.; m. p. and mixed m. p. 88—90°). The filtrates when treated with aqueous *cyclo*hexylamine afforded needles of di(*cyclo*hexylammonium) phenyl phosphate, m. p. 212° (decomp.; undepressed by admixture with an authentic specimen, m. p. 212° decomp.[18]).

Reaction of Cholesteryl Phenyl Hydrogen Phosphate with Acetic Acid.—The phenyl hydrogen phosphate (425 mg.) and acetic acid (6 c.c.) were refluxed for 27 hr. The product, treated as in the foregoing experiment, yielded 3β-acetoxycholest-5-ene (310 mg.; m. p. 112°) and di(*cyclo*hexylammonium) phenyl phosphate.

Reaction of Cholesteryl Diphenyl Phosphate with Acetic Acid.—The diphenyl phosphate (100 mg.) and acetic acid (3 c.c.) were refluxed for 24 hr. The product, treated as in the foregoing experiments, yielded 3β-acetoxycholest-5-ene (50 mg.; m. p. 113°) and *cyclo*hexylammonium diphenyl phosphate, m. p. and mixed m. p. 197—199° (Turnbull and Wilson [1]).

Synthesis of Cholesteryl Phenyl Hydrogen Phosphate.—Phenyl phosphorodichloridate (4·2 g.), 2 : 6-lutidine (2·7 g.), and benzene (10 c.c.) were mixed, and cholesterol (7·7 g.) in benzene (25 c.c.) gradually added. The mixture was warmed to 50°, stirred for 4 hr. at room temperature, and filtered from 2 : 6-lutidine hydrochloride (2·9 g.). The filtrate was divided into two equal portions (A and B). Portion (A) was washed with dilute hydrochloric acid, and refluxed for 30 min. with *iso*propyl alcohol (35 c.c.) and water (3 c.c.), and evaporated to dryness in a vacuum; the residue was crystallised first from benzene–light petroleum and then from ethyl acetate affording cholesteryl phenyl hydrogen phosphate (2·6 g.; m. p. 160—162° undepressed on admixture with a specimen prepared by the foregoing hydrolysis of the diphenyl phosphate). (B) was mixed with tetrahydropyran-2-ol (1·1 g.) and 2 : 6-lutidine (1·1 g.), and set aside for 40 hr. The product was evaporated leaving a syrup, presumably cholesteryl phenyl tetrahydropyran-2-yl phosphate, which was miscible with light petroleum, and decomposed at 100° during 2 hr. affording cholesteryl phenyl hydrogen phosphate (3·0 g.; m. p. and mixed m. p. 160°).

Synthesis of Cholesteryl Ethyl Hydrogen Phosphate.—Cholesterol (38·7 g.) in benzene (150 c.c.) was added to ethyl phosphorodichloridate (16·3 g.) and 2 : 6-lutidine (10·7 g.) in benzene (100 c.c.). The cloudy solution was warmed to 40°, set aside for 18 hr., and lutidine hydrochloride (12 g.) removed. *tert.*-Butyl alcohol (100 c.c.) was added, the solution refluxed for 30 min., water (4·0 c.c.) added, and the mixture evaporated in a vacuum. The residue was dissolved in excess of aqueous ethanolic potassium hydroxide, precipitated as a flocculent solid by acidification, dried, and recrystallised from benzene–light petroleum and then from ethyl acetate affording a *substance* as prisms (8·0 g.), m. p. 123—124° (Found: C, 76·1; H, 11·0; P, 3·2. Calc. for $C_{54}H_{91}O_4P,H_2O$: C, 76·1; H, 11·0; P, 3·6%). Titration of an aqueous ethanolic solution with aqueous potassium hydroxide (phenolphthalein) gave an equivalent weight of 852 (calc. for one acidic hydrogen, 853).

The mother-liquors from the foregoing recrystallisation were evaporated and treated with ethyl acetate, the solid (6·0 g.) was recrystallised from benzene–light petroleum then from ethyl acetate to give *cholesteryl ethyl hydrogen phosphate*, m. p. 155—158° (Found: C, 70·7; H, 10·2%; equiv., 480. $C_{29}H_{51}O_4P$ requires C, 70·4; H, 10·4%; equiv., 495).

Anhydro-(o-carboxyphenyl Phosphorochloridate).—Salicylic acid (69·0 g.) and phosphorus oxychloride (76·7 g.) were gradually heated to 150°, and maintained at 150° for 2 hr. The viscous product was distilled and the fraction, b. p. 116—125°/0·02 mm., crystallised from carbon tetrachloride affording prisms (39·6 g.), m. p. 90—93° (Found: C, 38·4; H, 2·2. Calc. for $C_7H_4O_4PCl$: C, 38·5; H, 1·85%). The substance is probably the same as that (m. p. 80°) described by Couper [13] and Anschütz.[18]

[13] Couper, *Compt. rend.*, 1858, **46**, 1107.
[18] Anschütz, *Annalen*, 1885, **228**, 308.

Cholesteryl o-Carboxyphenyl Hydrogen Phosphate.—The foregoing phosphorochloridate (8·0 g.) was dissolved in chloroform (30 c.c.), then 2 : 6-lutidine (4·0 g.) and cholesterol (14·2 g.) in chloroform (30 c.c.) were added. The mixture was set aside overnight, washed with water, dried (Na_2SO_4), and evaporated. The syrupy residue was diluted with benzene, excess of light petroleum added, and the precipitate crystallised from benzene–light petroleum affording the *phosphate* (2·6 g.), m. p. 141—142°, $[\alpha]_D$ −20° (ethanol), which was easily soluble in dilute aqueous sodium hydroxide (Found : C, 67·7; H, 8·5%; equiv. (by potentiometric titration), 296. $C_{34}H_{51}O_4P,H_2O$ requires C, 67·5; H, 8·8%; equiv., 302).

Reaction of Cholesteryl o-Carboxyphenyl Hydrogen Phosphate with Hydrogen Chloride.—The foregoing hydrogen phosphate (165 mg.) was dissolved in acetic acid (3 c.c.) and concentrated hydrochloric acid (0·3 c.c.) added. The solution was heated at 100° for 10 min. and diluted with water affording 3-β-chlorocholest-5-ene (m. p. 92—93°). The filtrates gave a strong purple coloration with aqueous ferric chloride.

Cholesteryl Phosphorodichloridate.—The crude pyridine-containing substance prepared from cholesterol (20 g.) by von Euler, Wolf, and Hellström's method [6] was extracted with hot light petroleum (b. p. 60—80°). The extracts deposited a solid which was recrystallised from light petroleum affording the phosphorodichloridate (7·5 g.), m. p. 110° (decomp.), $[\alpha]_D$ −31° [Von Euler, Wolf, and Hellström give m. p. 122° (decomp.)]

Cholesteryl Diphenyl Phosphate.—The foregoing phosphorodichloridate (530 mg.) was triturated with a solution of phenol (1 g.) and sodium ethoxide [from sodium (54 mg.) and ethanol (2 c.c.)]. Excess of dilute aqueous potassium hydroxide was added; the precipitate was recrystallised from aqueous acetone affording the diphenyl phosphate (520 mg.), m. p. 113° undepressed on admixture with a specimen prepared by Turnbull and Wilson's method.[1]

Cholesteryl Dihydrogen Phosphate.—Cholesterol (20 g.) was converted into the crude phosphorodichloridate by the foregoing method, and the product hydrolysed, without further purification, by refluxing it for 1¼ hr. with water (600 c.c.). The flocculent precipitate (A) was dissolved in aqueous potassium hydroxide (0·35N; 300 c.c.), and the solution filtered through Amberlite resin IR-120(H) and evaporated to complete dryness in a vacuum over phosphoric oxide. The residue was refluxed with benzene (200 c.c.) and water (2 c.c.) for 4 hr., the solution filtered and evaporated until crystallisation began. The product (10·7 g.) was recrystallised from a mixture of acetone and moist carbon tetrachloride affording irregular plates, m. p. 181° (decomp.), $[\alpha]_D$ −21° (ethanol) [Found : C, 69·5; H, 10·3%; equiv. (by titration), 229, 236. Calc. for $C_{27}H_{47}O_4P$: C, 69·5; H, 10·15%; equiv., 233).

The dihydrogen phosphate is insoluble in warm, dry benzene, carbon tetrachloride, or chloroform, but dissolves in the presence of water. Removal of the water by azeotropic distillation causes immediate precipitation of the substance. The dihydrogen phosphate, as thus prepared, is soluble in aqueous potassium hydroxide, but is insoluble in aqueous sodium hydroxide. A less soluble, metastable form, m. p. 187°, cf.[16] was obtained by rapid drying of its aqueous gel.

"Half" Pyridine Salt of Cholesteryl Dihydrogen Phosphate.—A portion of the solid (A) from the foregoing experiment was recrystallised from benzene affording the "half" pyridine salt, m. p. 178° (with sintering and darkening), $[\alpha]_D$ −36° (Found : C, 68·4; H, 9·8; N, 1·3. $2RO{\cdot}PO(OH)_2,C_5H_5N,H_2O$ requires C, 68·8; H, 9·9; N, 1·4%). An identical compound was obtained from pure cholesteryl dihydrogen phosphate and aqueous pyridine. The substance was recovered when its solution in aqueous potassium hydroxide was acidified with hydrochloric acid.

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[14] Biddiscombe, Coulson, Handley, and Herington, *J.*, 1954, 1957.
[15] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815.
[16] Neuberg and Jacobsohn, *Biochem. Z.*, 1928, **199**, 507.

883. *Phosphonic Polymers. Part I. The Copolymerisation of Diethyl Vinylphosphonate and Styrene.*

By C. L. Arcus and R. J. S. Matthews.

The monomer reactivity ratios for the copolymerisation of styrene (M_1) and diethyl vinylphosphonate (M_2) have been found to be $r_1 = 3{\cdot}25$ and $r_2 = 0$. The effects exerted by the phosphonic ester group on the course of vinyl polymerisation are discussed in the light of these values.

A study has been made of the relations between the phosphorus content, yield, and intrinsic viscosity of a copolymer and the temperature, initiator concentration, and initial monomer ratio at which it was prepared.

Weight-average molecular weights for a number of the copolymers have been determined by light-scattering measurements, and lie in the range 14,300—55,600.

Copolymers of diethyl vinylphosphonate, $CH_2{:}CH{\cdot}PO(OEt)_2$, and styrene have been prepared, and converted by hydrolysis into the corresponding vinylphosphonic acid–styrene copolymers (I), the properties of which are now being studied. It became clear,

$$\cdots\cdot CH_2{\cdot}CHPh{\cdot}CH_2{\cdot}CH(PO_3H_2)\cdot\cdots\cdot CH_2{\cdot}CHPh{\cdot}CH_2{\cdot}CH(PO_3H_2)\cdot\cdots\cdot \quad (I)$$

in the earlier stages of the investigation, that a quantitative study of the copolymerisation of diethyl vinylphosphonate with styrene was necessary. Accordingly, the reactivity ratios of these monomers have been determined, and relationships between copolymer properties and factors influencing copolymerisation have been ascertained.

Monomer Reactivity Ratios.—Styrene and diethyl vinylphosphonate being written as M_1 and M_2, respectively, and radical-chains ending in these units as $M_1^{\cdot}$ and $M_2^{\cdot}$, then, where the rate-constants of the reactions

$$M_1^{\cdot} + M_1 \longrightarrow M_1^{\cdot},\ M_1^{\cdot} + M_2 \longrightarrow M_2^{\cdot},\ M_2^{\cdot} + M_2 \longrightarrow M_2^{\cdot},\ M_2^{\cdot} + M_1 \longrightarrow M_1^{\cdot}$$

are respectively k_{11}, k_{12}, k_{22}, k_{21}, the monomer reactivity ratios, r_1 and r_2, are given by $r_1 = k_{11}/k_{12}$ and $r_2 = k_{22}/k_{21}$.

The graphical method described by Mayo and Walling [1] has been used.

It is desirable to remove monomers from copolymers prepared for the determination of monomer reactivity ratios by methods which do not involve the separation of fractions of differing composition. Accordingly, copolymerisation initiated by *tert.*-butyl hydroperoxide having been allowed to proceed to about 50% conversion, the monomers were removed by evaporation at reduced pressure, followed by a process in which the solvent was evaporated from a frozen benzene solution of the copolymer, yielding the latter as a porous solid which was finally evaporated to constant weight. Weights and phosphorus contents for four copolymers so prepared are recorded in Table 2; from these data the values $r_1 = 3{\cdot}25$ and $r_2 = 0$ have been calculated. Thus (when the monomers are present in equimolar concentrations) radical-chains $M_1^{\cdot}$ react 3·25 times as frequently with styrene as with diethyl vinylphosphonate, and radical-chains $M_2^{\cdot}$ react only with styrene.

Easy polymerisation of a monomer $CH_2{:}CAX$ is associated with a capacity of the substituent to accommodate a single electron in one or more canonical forms in addition to the form (II). Of the 33 ethylenic monomers whose relative reactivities are tabulated by Mayo and Walling,[1] the 12 most reactive yield radicals of form (III), which is capable of resonance-

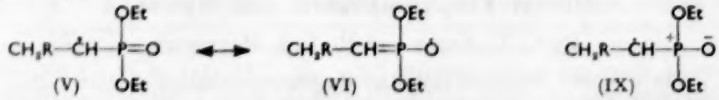
$$R^{\cdot} + CH_2{=}CAX \longrightarrow CH_2R{-}\dot{C}AX \quad (II)$$

$$(III)\ CH_2R{-}\dot{C}A{-}CB{=}Y \longleftrightarrow CH_2R{-}CA{=}C\dot{B}{-}Y \quad (IV)$$

stabilisation by formation of (IV). The activation energies of initiation and propagation are, presumably, reduced by the contribution which (IV) makes to the transition states in these processes. The formation of a structure analogous to (IV) by the radical (V), derived

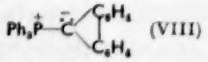
[1] Mayo and Walling, *Chem. Reviews*, 1950, **46**, 191.

from diethyl vinylphosphonate, requires the formation of a carbon–phosphorus double bond (as in VI) :



(V) (VI) (IX)

(It can be shown that other forms, in which the single electron is placed on the ethoxyl oxygen, or on phosphorus, all involve a C=P bond.) However, a search has revealed a record of only one compound formulated as containing such a bond, the pentaphenyl compound (VII).[2] The analogous fluorenyl compound (VIII) is formulated by Pinck and Hilbert [3] as a phosphonium zwitterion. It is inferred that there is an obstacle to the formation of carbon–phosphorus double bonds, the nature of which is not discussed here. It follows that the phosphonic ester group is incapable of stabilising, and facilitating the formation of, radical (V) by resonance. [Use of formula (IX), in which oxygen is bonded to phosphorus by a co-ordinate link, does not affect the above conclusion, a C=P double bond again being necessary to render C_α four-covalent.]

(VII) $Ph_3P{=}CPh_3$  (VIII)

The addition of a molecule of diethyl vinylphosphonate therefore requires attack by a radical of greater than average energy. The radical so formed then reacts, virtually invariably since $r_2 = 0$, with styrene. Inspection of scale models of a diethyl vinylphosphonate radical-chain end, and of diethyl vinylphosphonate monomer, shows that it is sterically possible for the two to approach closely, but that, in the conformations required for such approach, the oxygen atoms of the two phosphonate groups are brought into close proximity. Hence, electrostatic repulsion may oppose reaction between a diethyl vinylphosphonate radical-chain end and a molecule of diethyl vinylphosphonate monomer. In addition to this effect, another, tending to the same result, may operate; this arises from the polarisability of monomer molecules, and has been invoked [4, 5] to explain instances of alternate copolymerisation. A radical terminated by the electron-attracting phosphonic ester group may react preferentially with styrene, which bears a phenyl group capable of electron-release of the $+E$ type, rather than with diethyl vinylphosphonate, which bears an electron-attracting substituent.

The values of r_1 and r_2 found for the copolymerisation of styrene and diethyl vinylphosphonate are approximately paralleled by those which have been recorded by Price and Zomlefer,[6] and by Doak,[7] for the copolymerisation of styrene and methyl vinyl sulphone : $r_1 = 2{\cdot}0$, $r_2 = 0{\cdot}01$, and $r_1 = 2{\cdot}4$, $r_2 = 0{\cdot}0$, respectively. If the radical (X), derived from methyl vinyl sulphone, were to be stabilised by resonance with a form analogous to (IV), then the structure (XI) is required. No record has been found of compounds in which carbon is doubly bonded to sulphur when the latter is other than bivalent, whence it is concluded that the bonding of (XI) is improbable, and that the sulphone group is unable to facilitate the formation, or increase the stability, of (X) by contributing the resonance form (XI).

(X) (XI)

Factors controlling Copolymerisation.—A study has been made of the relations between the phosphorus content, yield (expressed as conversion of total monomer), and intrinsic viscosity of a copolymer and the temperature, initiator concentration, and initial monomer

[2] Staudinger and Meyer, *Helv. Chim. Acta*, 1919, **2**, 635.
[3] Pinck and Hilbert, *J. Amer. Chem. Soc.*, 1947, **69**, 723.
[4] Bartlett and Nozaki, *ibid.*, 1946, **68**, 1495.
[5] Walling, Briggs, Wolfstirn, and Mayo, *ibid.*, 1948, **70**, 1537.
[6] Price and Zomlefer, *ibid.*, 1950, **72**, 14.
[7] Doak, quoted in ref. 3, but apparently not yet published.

ratio at which it is formed, with the object of delimiting the conditions under which copolymers of given characteristics may be prepared. On the basis of preliminary experiments, there was selected as an " origin " the copolymer formed after 11 hr. at 116° from a mixture of diethyl vinylphosphonate and styrene in molar ratio 1 : 3, containing 1·65% of *tert.*-butyl hydroperoxide; from this point the temperature, initiator concentration, and initial monomer ratio of copolymerisation were varied.

Preliminary experiments had also shown there to be some variation in yield and intrinsic viscosity, but not in phosphorus content, of copolymers prepared under identical conditions from different specimens of diethyl vinylphosphonate. Two complete series of experiments were therefore carried out, both with diethyl vinylphosphonate from one preparation, portions of which were redistilled for each series; the reaction mixtures for each study of a variable (*e.g.*, temperature) were prepared at one time, and heated within a short time of preparation. The removal of monomer by prolonged evaporation, which was used in the determination of monomer reactivity ratios, was replaced in the present experiments by precipitation of the copolymer on addition of its solution in ethyl acetate to methanol. Precipitation necessarily involves a degree of fractionation. There is some removal of copolymer which is relatively high in phosphorus, owing to the circumstance that phosphonic ester groups are more hydrophilic than phenyl groups. Also, copolymer of low molecular weight is removed; a plot of conversion *versus* $[\eta]_c$ for all copolymers shows a relatively abrupt lower termination at $[\eta]_c = 0{\cdot}10$. The reported conversions are, therefore, those to copolymer of molecular weight sufficient to give $[\eta]_c > 0{\cdot}10$.

Intrinsic viscosities, $[\eta]_c$, of 1% solutions of the copolymers in toluene at 25° were determined, and (see p. 4611) do not differ appreciably from the limiting intrinsic viscosities.

The results obtained are recorded in Figs. 1, 2, and 3; the points relating to the " origin " appear in each Figure.

Temperature.—The extent of copolymerisation of diethyl vinylphosphonate, measured by the phosphorus content of the copolymer, varies little with temperature: the phosphorus contents of copolymers prepared at 100°, 116°, and 133° are near 2·6%, those of copolymers prepared at 80° and 154° are somewhat lower. The intrinsic viscosity falls with increase in copolymerisation temperature, and approaches the minimum of 0·10. Conversion attains a maximum at about 112°, then falls rapidly with increasing temperature, the fall being correlated with the approach of the intrinsic viscosity to the minimum value for precipitation.

Initiator Concentration.—Variation in the initial concentration of *tert.*-butyl hydroperoxide over the range 0·75—5·1% has little effect on the phosphorus content of the copolymer, there being a slight fall with increase in catalyst. In both series intrinsic viscosity falls with increase in catalyst; each series is self-consistent, but in the second the values are higher than in the first. Conversion also falls with increase in catalyst, the more marked fall in the first series being correlated with the approach of $[\eta]_c$ to the value 0·10.

TABLE 1. *Weight-average molecular weights of diethyl vinylphosphonate–styrene copolymers.*

Copolymer *	$\overline{M}$	$([\eta]_c/k)^{1/a}$	Copolymer	$\overline{M}$	$([\eta]_c/k)^{1/a}$
3a	38,500	34,900	16a	36,400	33,400
5b	40,000	35,650	19a	14,700	14,900
6a	29,400	26,100	21a	14,300	14,000
7a	28,200	27,300	27a (i)	28,200	27,500
11b	33,900	34,700	27a (ii)	27,400	27,500
12a	16,000	15,600	28b	55,600	57,300
14a	38,500	38,600	29a	45,400	44,400

* Nos. 3—12, 14—21, 27—29 refer respectively to copolymerisation with initiator, temperature, and monomer-ratio variation, and a and b to the 1st and 2nd series.

Initial Ratio of Monomers.—An increase of 1 to 9 in the molar ratio of styrene to diethyl vinylphosphonate in the initial mixture of monomers resulted in the formation of copolymers containing from 4·5 to 1·5% of phosphorus, equivalent to the presence in the copolymers of 5·0 to 18·6 styrene units per unit of diethyl vinylphosphonate. Intrinsic viscosity (one anomolous value excepted) increases with the styrene content of the copolymers. The

conversion into copolymer of molecular weight sufficient for precipitation increases markedly with the styrene content.

Molecular Weights.—The weight-average molecular weights, $\overline{W}$, of a number of the copolymers have been determined (Table 1) by light-scattering measurements, the procedure and method of calculation for which are described in the Experimental section. The values of $\overline{W}$ and $[\eta]_c$ for the copolymers of Table 1 are approximately related by the empirical equation $[\eta]_c = k\overline{W}^{\alpha}$, where $k = 5{\cdot}90 \times 10^{-5}$ and $\alpha = 0{\cdot}7785$, and values of $\overline{W}$ calculated from $[\eta]_c$ by its use are given in Table 1.

FIG. 1.

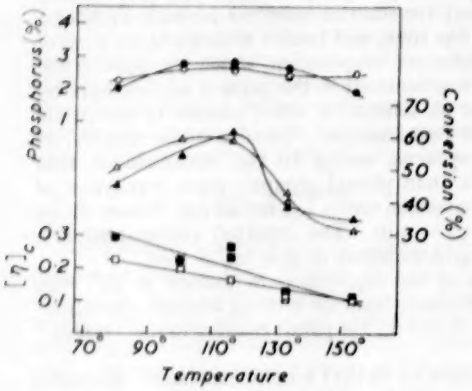


FIG. 2.

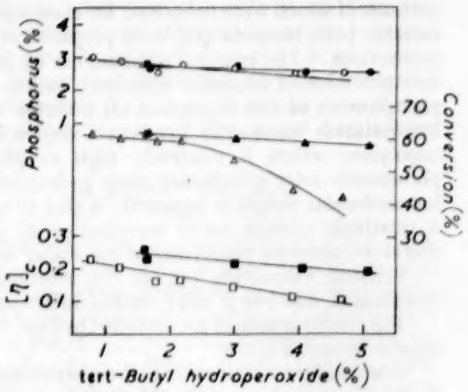
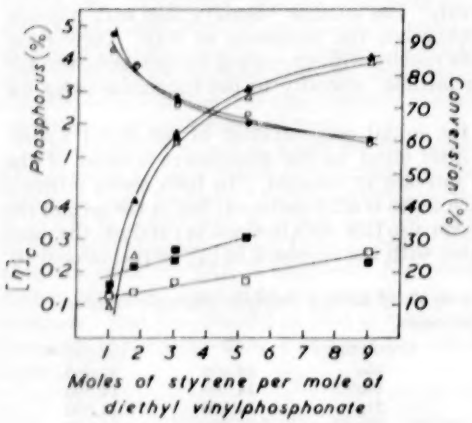


FIG. 3.



Copolymerisation of diethyl vinylphosphonate and styrene.

○ Phosphorus content of copolymer.
△ Conversion of total monomer.
□ Intrinsic viscosity of copolymer.

"Open" points, first series; "solid" points, second series.

EXPERIMENTAL

Diethyl 2-bromoethylphosphonate was prepared in 58% yield from triethyl phosphite and ethylene bromide, and converted in 87% yield into diethyl vinylphosphonate, by Kosolapoff's methods.[8] Diethyl vinylphosphonate had b. p. 72—75°/2·5 mm., n_D^{25} 1·4262; on hydrogenation, in ethanol with platinum oxide catalyst, it absorbed 100·1% of the calculated quantity of hydrogen.

Styrene was thrice washed with N-sodium hydroxide and thrice with water, dried ($CaCl_2$), and distilled at room temperature under 0·2 mm. pressure, the receiver being cooled in a solid

[8] Kosolapoff, *J. Amer. Chem. Soc.*, 1948, **70**, 1971.

carbon dioxide–methanol bath. *tert.*-Butyl hydroperoxide was prepared by Davies, Foster, and White's method.[9]

Determination of Monomer Reactivity Ratios.—The quantities of diethyl vinylphosphonate and styrene shown in Table 2 were weighed into the flask *A* (Fig. 4), and *tert.*-butyl hydroperoxide (1% of the weight of monomers) was added. The air in flask *A* was displaced by nitrogen, and the stoppered flask was maintained at 116°, by means of *n*-butanol boiling under reflux in the flask *B*, until it was estimated that 50% of the reaction mixture had polymerised. Flask *A* was then connected, through three traps cooled in solid carbon dioxide–methanol, to a vacuum pump, and the butanol in *B* was replaced by acetone; flask *A* was then kept under 0·5 mm. pressure at 56° until it attained constant weight. Benzene (10 ml.) was added to the contents of *A*; the copolymer dissolved, and the solution was frozen by immersion in solid carbon dioxide–methanol. Flask *A* was then immersed in ice, and the benzene was sublimed at 0·5 mm., yielding the copolymer as a white, highly porous material. It was again kept at 56°/0·5 mm. until it attained constant weight. The total time required for the removal of the monomers by pumping varied from 17 to 227 hr., increasing with the mole-fraction of diethyl vinylphosphonate in the reaction mixture. Phosphorus contents of the copolymers were determined by the method described below, and are recorded, together with the weights of the copolymers, in Table 2.

FIG. 4.

Preparation of Copolymers with Variation of Temperature, Initiator Concentration, and Initial Monomer Ratio.—Styrene, diethyl vinylphosphonate, and *tert.*-butyl hydroperoxide, in the proportions given in Figs. 1, 2, and 3 (total quantity 2 g.), were weighed into Pyrex-glass tubes; after displacement of air by nitrogen, the tubes were sealed and heated for 11 hr. in a jacket containing the vapour of one of the following liquids, boiling under reflux at the stated temperature: benzene (80°); water (100°); *n*-butanol (116°); ethylbenzene (133°); anisole (154°). Each tube was then splintered under ethyl acetate (20 ml.), the solution of copolymer was filtered, and the glass residue washed with ethyl acetate (2 × 5 ml.); the filtrate and washings were added slowly with stirring to methanol (225 ml.), residual polymer solution being washed in with a further portion of ethyl acetate (15 ml.). The precipitated copolymer was collected on a sintered-glass crucible, washed with methanol (4 × 50 ml.), dried *in vacuo* (over $CaCl_2$), and weighed. Intrinsic viscosity, weight-average molecular weight by light-scattering, and phosphorus content were determined by the following methods.

TABLE 2.

Copolymer	Styrene (g.)	Diethyl vinylphosphonate (g.)	Copolymer (g.)	P (%)
1	1·8435	0·2102	1·7101	1·10
2	1·3040	0·5069	1·2001	2·86
3	1·1106	0·7573	1·0589	3·64
4	1·0061	1·0497	1·0518	4·88

Intrinsic Viscosity.—The intrinsic viscosity, $[\eta]_c = (1/c) \ln (\eta_{soln.}/\eta_{solv.})$, where c = g. of polymer in 100 ml. of solution, of a 1% solution of the copolymer in toluene was determined at 25°. Of selected copolymers, 2% solutions were made, whence 1% and 0·5% solutions were prepared by dilution; their intrinsic viscosities are recorded in Table 3. It is seen that the intrinsic viscosities at $c = 1$ do not differ appreciably from the limiting values implied by the data.

TABLE 3.

Copolymer	c	$[\eta]_c$	Copolymer	c	$[\eta]_c$	Copolymer	c	$[\eta]_c$	Copolymer	c	$[\eta]_c$
8a	2·021	0·150	13b	2·061	0·196	2a	2·082	0·227	29a	2·012	0·254
	1·011	0·149		1·031	0·198		1·041	0·232		1·006	0·262
	0·505	0·149		0·516	0·195		0·521	0·231		0·503	0·264

Molecular Weight by Light-scattering.—Measurements were made with a Brice-Phoenix light-scattering photometer; light of wavelength 546·1 × 10^{-7} cm. from a high-pressure stabilised mercury lamp was used throughout. The solutions for measurement, which were prepared by

[9] Davies, Foster, and White, *J.*, 1953, 1545.

dilution of a 1% solution of the copolymer in toluene, were filtered under pressure through a No. 5-on-3 sintered-glass filter directly into the photometer cell. Refractive-index differences between solution and solvent were measured in a Rayleigh differential refractometer.

To a good approximation $Hc/\tau = 1/\overline{W} + 2Bc$, where τ is the absolute turbidity, c is the concentration of the solution in g./ml., $\overline{W}$ is the weight-average molecular weight, and B is a constant depending on the solvent; μ_0 being the refractive index of the solvent and μ that of the solution for $\lambda = 546{\cdot}1 \times 10^{-7}$ cm., we have

$$H = 6{\cdot}18 \times 10^{-6} \times \mu_0^2 (\mu - \mu_0)/c^2$$

For each copolymer, values of τ and H were calculated for each solution measured; Hc/τ was then plotted against c, and the intercept on the former axis was equal to the reciprocal of the copolymer weight-average molecular weight.

Determination of Phosphorus.—" AnalaR " inorganic reagents were used. The whole of the copolymer specimen was finely ground by means of a stainless-steel mortar and pestle (the copolymer becomes electrified and scatters in, *e.g.*, an agate mortar). The copolymer (20 mg.), was heated with perchloric acid (72%, 5 ml.) in a small Kjeldahl flask, very gently for 10 min., thereafter more strongly until the solution was boiling; after 30 min. it had become colourless, and heating was continued for a further few minutes until it fumed. Phosphorus was determined as orthophosphate by the following modification of Allen's method.[10]

Amidol (50 g.), in solution in water (125 ml.), was heated with charcoal (1 g.) and filtered; ethanol (100 ml.) was added and the whole was chilled. The colourless crystals of amidol were filtered off, washed with ethanol, and dried *in vacuo*. The reagent solution was prepared daily as follows: to a solution of amidol (1·0 g.) and sodium sulphite ($Na_2SO_3,7H_2O$; 20 g.) in water (60 ml.), sulphuric acid (2·7 ml.) in water (20 ml.) was added. Amidol and the solution were kept in brown glass bottles.

Ammonium molybdate (4·15 g.) was dissolved in water (50 ml.).

The cold perchloric acid solution (above) was diluted with water to 250 ml.; to 25 ml. of this solution were added perchloric acid (72%; 3·5 ml.), amidol reagent (4·5 ml.), and ammonium molybdate solution (3·5 ml.), in that order, and the whole was diluted to 50 ml. with water, and shaken. After 30 min. the absorption of the solution was measured in a Spekker absorptiometer (1 cm. cell; filters having a peak transmittance at 700 mμ), and that of a blank solution of reagents with water was also determined. From the difference (solution reading − blank reading) the phosphorus content was read from a graph (a straight line) plotted from the similarly-determined readings derived from a series of solutions of potassium dihydrogen phosphate.

The oxidative degradation and colorimetric determination were carried out in quadruplicate for the monomer reactivity ratio copolymers, and in duplicate for the copolymers from experiments in which the variables were studied. The arithmetic mean difference between pairs of duplicate determinations was 0·07% of P, and the average difference of one of quadruplicate determinations from the mean of the set was 0·07% of P.

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Battersea Polytechnic, London, S.W.11. [*Received, June 18th*, 1956.]

[10] Allen, *Biochem. J.*, 1940, **34**, 858.

884. *The Reaction between Phosphorus Trichloride and Bromine. Part I.*

By G. S. Harris and D. S. Payne.

A cryoscopic study of the system phosphorus trichloride–bromine in nitrobenzene has shown the existence of two equilibria involving PX_5 and PX_7 species. Results of the conductometric titration of nitrobenzene and phosphoryl chloride solutions of phosphorus trichloride and bromine are given and discussed. The compositions of two solids obtained from carbon tetrachloride solution of the components are reported.

The recent publication by Popov and his co-workers [1] on the phosphorus trichloride–bromine system prompts us to publish the following account of our work on this system. Further studies are intended.

Studies of the reaction between bromine and phosphorus trichloride can be grouped in three historical periods. During the first two (1847—1886 and 1928—1934) the aim was primarily the synthesis of definite bromide-chlorides of phosphorus(V), but despite numerous investigations, the reaction was far from being understood or the products clearly identified, and this was the position at the commencement of the third period in 1951. Since then, three groups, including ourselves, have sought to clarify the position, for it appeared that the evidence for the many individual compounds which had been reported was scanty and often contradictory. Various compositions of the solid phases, including PCl_3Br_2, have been reported, but, in general, the analytical data are poor and there is much confusion concerning the properties.

More recently, Fialkov and Kuz'menko [2a] have examined the phosphorus trichloride–bromine system by thermal analysis and have recognised in the phase diagram two maxima corresponding to the compositions PCl_3Br_4 and PCl_3Br_{18}. They have also reported the isolation of compounds corresponding to these compositions. It appears that the liquid phases corresponding to these compositions are good conductors of electricity ($\kappa_{35°} = 1{\cdot}82 \times 10^{-4}$ and $\kappa_{25°} = 8{\cdot}01 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$ respectively). However, in the solid state only the phase with composition PCl_3Br_{18} has an appreciable conductance ($\kappa_{20°} = 1{\cdot}53 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$). Further work [2b] on the viscosity–composition relationships in this system showed the possible existence of another compound, PCl_3Br_8.

Conductance and transport experiments were carried out on the system in nitrobenzene, and on the basis of the results the compounds are assigned quasi-phosphonium structures, $[PCl_3Br]^+[Br(Br_2)_n]^-$, where n has values of 1, 2, and 8 in the compounds described. A series of equilibria between these forms is envisaged in which the higher conductances observed, as the ratio of bromine to phosphorus trichloride is increased, are attributed to the increasing concentration of a species undergoing ready electrolytic dissociation. However, the very high effective concentration employed, *e.g.*, 0·4—50M in nitrobenzene, makes comparison with other workers' results difficult and uncertain. Popov and his co-workers [1] have found that the system does not yield stable solid phases corresponding to simple formulæ. For example, direct reaction of phosphorus trichloride and bromine led to an unstable aggregate of composition $PCl_{3\cdot0}Br_{5\cdot7}$, which under reduced pressure yielded a stable mixed halide with the empirical formula $PCl_{4\cdot67}Br_{0\cdot33}$ (shown to have a face-centred cubic cell corresponding to $P_{12}Cl_{56}Br_4$ per unit cell). It is suggested that this unit cell is built up from 8 PCl_4^+, 4 PCl_6^-, and 4 Br^- units. Absorption spectra of phosphorus trichloride–bromine mixtures in carbon tetrachloride and in nitrobenzene have not revealed the presence of complexes in these solvents.

We have examined the system in solvents which, from previous work with phosphorus pentachloride and pentabromide,[3,4] are known to be suitable for this type of compound. However, preliminary experiments showed that acetonitrile, although suitable for the

[1] Popov, Geske, and Baenziger, *J. Amer. Chem. Soc.*, 1956, **78**, 1793.
[2] Fialkov and Kuz'menko, *Zhur. obshchei Khim.*, (*a*) 1951, **21**, 433; (*b*) 1952, **22**, 1290, 1335.
[3] Payne, *J.*, 1953, 1052.
[4] Harris and Payne, following paper.

simple pentahalides, is not stable with the phosphorus trichloride–bromine system. The course of conductometric titrations of phosphorus trichloride against bromine both in nitrobenzene and in phosphoryl chloride solution showed a definite increase in conductance but no marked inflections. In phosphoryl chloride solutions the molar conductances calculated at definite mole ratios were not substantially greater than those of the phosphorus trichloride and bromine separately. At the concentrations employed (*ca.* 0·015M) it is clear that in neither of these solvents is the stabilisation of an ionic species favoured; however, the slight increase in conductance observed in the course of the titrations is more than would be expected for simple mixing of the component solutions without any interaction.

In view of the low electrolytic conductances of these solutions we studied them cryoscopically, and ignored ionisation in interpreting the results. Of the solvents carbon tetrachloride, phosphoryl chloride, and nitrobenzene, only the last was suited to such a study. The freezing-point depressions, determined for various ratios of phosphorus trichloride to bromine and plotted against the mole ratio, gave a straight line and thus depressions were obtained for the whole-number ratios of 1 : 1, 1 : 2, and 1 : 3 of phosphorus trichloride to bromine. From these were calculated values of the equilibrium constants of various equilibria considered singly and in combination. The results could be completely described by the two equilibria :

$$PX_3 + X_2 \rightleftharpoons PX_5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

$$PX_3 + 2X_2 \rightleftharpoons PX_7 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

where X is chlorine or bromine in this treatment. The corresponding equilibrium constants were, for (i), $K_{5\cdot70^\circ} = 1\cdot43$ mole^{-1} l., and, for (ii), $K_{5\cdot70^\circ} = 5\cdot45$ mole^{-2} l.^{2}. Table 1 shows the values of α_1 and α_2, the degrees of association corresponding to the equilibria (i) and (ii) at whole-number mole ratios.

TABLE 1.

Mole-ratio PCl_3 : Br_2	α_1	α_2	α_1/α_2
1 : 1	0·09036	0·02492	3·625
1 : 2	0·1560	0·08379	1·861
1 : 3	0·1940	0·1552	1·249

Concentration of PCl_3 = 0·0839M.

No other equilibria considered yielded constant values of the equilibrium constants with varying mole ratio. Thus the nitrobenzene solution contains, in addition to phosphorus trichloride and bromine and exceedingly small amounts of ionised species, equilibrium amounts of a PX_5 and a PX_7 species. The failure [1] of the spectrophotometric method to reveal the existence of these complexes is an indication of the close similarity of the spectra of these complexes to that of the free halogen and also an indication of the looseness of the binding in the complexes.

Attempts to repeat the isolation of solid phases in this system were carried out by using solutions of the components in suitable solvents. Only in the system phosphorus trichloride–bromine–carbon tetrachloride was solid material containing phosphorus halide obtained and this contained carbon tetrachloride of crystallisation. The analytical data correspond fairly well to the compositions PCl_3Br_7,CCl_4 and $PCl_3Br_7,2CCl_4$. (Thanks are due to a Referee for drawing attention to this formulation.) However, the analytical figures for chlorine and bromine are not very reliable and the possibility that these compounds are members of the PCl_3,nBr_2 series previously reported by Fialkov and Kuz'menko [2a] cannot be excluded. Attempts to remove the carbon tetrachloride led to loss of bromine. The second compound resulted from an attempt to prepare PCl_3Br_4 by Fialkov's method.[2a]

Little is known of the factors which influence the stability of molecular complexes such as PX_5 and PX_7 in nitrobenzene solution. Craig *et al.* [6] have suggested that the use of 3*d*

[5] Craig, Maccoll, Nyholm, Orgel, and Sutton, *J.*, 1954, 332.
[6] Smith and Witten, *Trans. Faraday Soc.*, 1951, **47**, 1304.

orbitals by phosphorus will only be likely when the group is effectively strongly electronegative, in keeping with the known stability of the simple phosphorus pentahalides. The formation of the complexes in the phosphorus trichloride–bromine system would not be expected to involve a simple molecule, with bonds involving 3*d* orbitals, in view of the electronegativity of bromine and the well-substantiated instability of mixed halides of both ter- and quinque-valent phosphorus. These mixed halides disproportionate readily as has been observed by Popov in this particular system.[1] The experiments described here cannot distinguish a disproportionation reaction with certainty, but the low electrolytic conductance in the nitrobenzene (Λ_m = *ca.* 0·2; cf. Λ_m for phosphorus pentachloride = *ca.* 3 at comparable concentrations) shows that conversion into phosphorus pentachloride, if it occurs at all, must be to an extent less than about 10%. The possibility that a system involving phosphorus tribromide and chlorine may be set up to any appreciable extent is eliminated by the fact that the colour of the solution did not change appreciably, in the course of the experiment, from that which would be expected of a solution of pure bromine of corresponding concentration. From a general survey of all the compounds reported in the phosphorus trichloride–bromine system under a variety of conditions, it is clear that the ability of bromine, in contrast to chlorine and fluorine, to form polybromides is an important feature. Whether this class of compound contains a polyhalogeno-anion and a phosphorus halogeno-cation, as suggested by Fialkov and his co-workers, or a more complex but less definite formulation as in a loose association of a trichloride molecule and one or more bromine molecules, we hope to decide by further work.

Experimental

Materials.—A commercial specimen of phosphorus trichloride was fractionated at a reflux ratio of about 15 to 1 in a two-foot column packed with Fenske rings. The fraction, b. p. 74·4—74·5°, was taken for further purification by repeated fractionation in a vacuum line. The pure compound was stored in sealed ampoules. Bromine (" AnalaR ") was carefully fractionated in an all-glass system *in vacuo* and stored in sealed ampoules. Acetonitrile was purified by Smith and Witten's method.[7] Carbon tetrachloride (" AnalaR ") was distilled from phosphoric oxide before use. 1 : 4-Dioxan was refluxed for 14 hr. over sodium, then distilled and used directly (b. p. 101·0°). Ethylene dichloride (B.D.H.) was shaken with portions of concentrated sulphuric acid until the acid layer remained colourless. This was followed by washing with water and then with several portions of a sodium hydrogen carbonate solution. After preliminary drying (Na_2SO_4), the material was further dried by azeotropic distillation, and the dry fraction then refluxed with an excess of phosphoric oxide and finally distilled twice from further portions of phosphoric oxide (b. p. 83—83·5°/755 mm.). Nitrobenzene was washed with 5*N*-sulphuric acid and then with water, followed by repeated washings with saturated aqueous sodium hydroxide solution until the aqueous layer was colourless. The washing was completed by repeated extraction with water until the aqueous layer was neutral to litmus. The nitrobenzene was stored for several days over 14—20-mesh calcium chloride and then after filtration was distilled at atmospheric pressure (b. p. 208—210°). Further purification was achieved by repeated fractional freezing, and the liquid was finally distilled *in vacuo*, and a middle fraction taken (b. p. 64—68°/*ca.* 2 mm.). Phosphoryl chloride was distilled several times through a short column, and the middle fraction of the final distillate was taken for use (b. p. 105·4—105·8°).

Conductometric Titrations.—The experiments were carried out in the apparatus described previously.[7] Solutions were prepared by breaking a bulb containing a known weight of the solute under a known weight of solvent. In each case the bromine solution was the titrant. The conductance rose on addition of the bromine solution and the resulting value was then observed to be constant for at least 1 hr. Such reaction as occurs is thus instantaneous and the resulting products are stable within the time of observation. With nitrobenzene as solvent values for the molar conductance measured at room temperature were, for mole ratio phosphorus trichloride to bromine 1 : 1, Λ_m = 0·1088 ohm^{-1} cm.^{2} mole^{-1}, c_m = 0·01837; for 1 : 2, Λ_m = 0·2132, c_m = 0·01642; for 1 : 3, Λ_m = 0·3305, c_m = 0·01483, and for 1 : 4, Λ_m = 0·4362, c_m = 0·01353. For phosphorus trichloride alone Λ_m = 0·0099 at c_m = 0·01837 and for bromine alone Λ_m = 0·056 at c_m = 0·03608, measured in nitrobenzene solution at room temperature.

[7] Harris and Payne, *J.*, 1956, 3038.

With phosphoryl chloride as solvent the values for the molar conductance measured at room temperature were for mole ratio phosphorus trichloride to bromine 1 : 1, $\Lambda_m = 0{\cdot}031$, $c_m = 0{\cdot}0137$, and for 1 : 2, $\Lambda_m = 0{\cdot}046$, $c_m = 0{\cdot}0123$. For phosphorus trichloride alone $\Lambda_m = 0{\cdot}023$, $c_m = 0{\cdot}0244$, and for bromine alone $\Lambda_m = 0{\cdot}013$, $c_m = 0{\cdot}0325$ measured in phosphoryl chloride solution at room temperature.

Cryoscopic Experiments.—The cryoscopic cell was an all-glass modification of the Beckmann apparatus, designed to exclude atmospheric moisture. Three attachments pass through the stopper (a B45 cone) of the apparatus; these are a thermometer pocket, a vertical stirrer guide, and a chute *cum* ampoule breaker for the introduction of known amounts of solute. Stirring is accomplished by means of a coil of thin glass surrounding the thermometer pocket. Attached to the upper end of the stirrer and situated within the stirrer guide is a glass-enclosed soft-iron rod which allows of magnetic operation. The cell, containing solvent (*ca.* 80 ml.), was placed in an air jacket, which was in turn placed in the cooling bath. When the freezing point of pure solvent had been found, phosphorus trichloride was introduced, and the freezing point redetermined. Bromine was then added in stages, and the freezing point of the solution determined after each addition. The contributions from the various postulated equilibria were derived by a graphical treatment of the results. The experimental results are shown in Table 2.

TABLE 2.

Mole ratio, $Br_2 : PCl_3$	0·000	0·4568	0·9261	1·4525	1·8729	2·3004	2·7648	3·0186
F. p. (relative)	5·194°	4·981°	4·786°	4·585°	4·409°	4·250°	4·086°	3·993°

F. p. of pure solvent = 5·684° (relative). F. p. of 0·0839M-PCl_3 solution = 5·194° (relative).

Attempts to prepare an Adduct of Phosphorus Trichloride and Bromine.—Solutions containing phosphorus trichloride and bromine in the mole ratio 1 : 1 were prepared in various solvents (the concentration of these solutions was always about 0·5M). In acetonitrile mixing of the reactants was accompanied by evolution of heat, and on standing the colour of the solution diminished to a pale yellow. Examination showed that reaction with the solvent had occurred. In nitrobenzene no heat was evolved on mixing the reactants and the colour remained undiminished after standing for several weeks. Cooling the solution failed to bring about crystallisation of any solid other than solvent. Similar results were obtained with phosphoryl chloride and ethylene dichloride. 1 : 4-Dioxan gave only a precipitate of the crystalline bromine addition compound, $C_4H_8O_2Br_2$, m. p. 66°, mixed m. p. with an authentic specimen 67—68°. In carbon tetrachloride, on mixing of the reactants, there was no liberation of heat but two deep red layers separated, the lower being slightly the darker. Additional solvent was added until the solution was homogeneous, and the solution cooled to 2°. After 24 hr. dark red crystals had formed in the solution and on the walls of the vessel above the level of the liquid. The crystals had m. p. 15—16°, the same as that of the lower layer observed when the original solution was prepared. The solid was carefully separated from solution without allowing it to melt or to come into contact with atmospheric moisture [Found: P, 3·65; Br, 65·30; Cl, 14·02; CCl_4 (by diff.), 17·03. Calc. for PCl_3Br_7,CCl_4: P, 3·64; Br, 65·77; Cl, 12·51; CCl_4, 18·09%. Calc. for $PCl_3Br_6CCl_4$: P, 4·02; Br, 62·22; Cl, 13·80; CCl_4, 19·96%]. The carbon tetrachloride was liberated and identified on hydrolysis of the solid. Fialkov [3a] describes the preparation, by the direct reaction of an excess of phosphorus trichloride with bromine, of a solid of composition PCl_3Br_4, which could be crystallised from carbon tetrachloride. Careful repetition of the method yielded a dark red solid which on hydrolysis and analysis gave a quantity of carbon tetrachloride corresponding to 29·9% of the original solid and a total halide corresponding to 8·10 ml. of N-silver nitrate per g. of solid (Calc. for $PCl_3Br_7,2CCl_4$: CCl_4, 30·63%; N-$AgNO_3$, 9·96 ml. Calc. for $PCl_3Br_6,2CCl_4$: CCl_4, 33·28%; N-$AgNO_3$, 9·73 ml.). Both solids had low m. p. and readily lost carbon tetrachloride and bromine.

Analyses.—Phosphorus was determined by oxidation of the hydrolysate and the subsequent precipitation of the phosphate as magnesium ammonium phosphate, followed by ignition at 900° to magnesium pyrophosphate. Total halogen was determined by Volhard's method. Bromide in the presence of chloride was determined by the method of Kolthoff and Yutzy.[9]

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THE UNIVERSITY, GLASGOW, W.2. [*Received, June 22nd*, 1956.]

[9] Kolthoff and Yutzy, *Ind. Eng. Chem. Anal.*, 1937, **9**, 75.

885. *Non-aqueous Solutions of Phosphorus Pentabromide.*

By G. S. Harris and D. S. Payne.

Solutions of phosphorus pentabromide in acetonitrile are electrolytically conducting; the values of molar conductance are reported. The ions present are PBr_4^+ and PBr_6^-. By cryoscopy it has been shown that the system phosphorus tribromide–bromine in nitrobenzene can be described by two equilibria, involving PBr_5 and PBr_7 species.

In continuation of our studies [1, 2] on phosphorus(v) halides, we have investigated non-aqueous solutions of phosphorus pentabromide and the system phosphorus tribromide–bromine, to obtain information about the nature of the solute species. This is of interest since it has been established independently by Powell and Clark [3] and Van Driel and McGillavry [4] that the lattice of crystalline phosphorus pentabromide is built up from $[PBr_4]$ and [Br] units, which are considered as unipositive and uninegative ions respectively. It would be expected therefore that phosphorus pentabromide, in suitable solvents (chemically inert and of high dielectric constant), would behave as a salt and produce electrolytically conducting solutions. This is so for phosphorus pentabromide in arsenic trichloride,[5] sulphur dioxide,[5] bromine,[6] and nitrobenzene.[7] Some data are given in the literature of the molar conductance of these solutions, but the suggested schemes of ionisation are essentially hypothetical and involve a P^{5+} or solvated P^{5+} cation. Bromine solutions of phosphorus pentabromide have been investigated by Finkelstein,[8] who found that electrolysis suggested the presence of a complex positive ion on account of the tendency of phosphorus pentabromide to polymerise in bromine solution.[9]

The molecular dissociation of phosphorus pentabromide, $PBr_5 \rightleftharpoons PBr_3 + Br_2$, as it occurs in solvents of low dielectric constant, has also been studied. Kastle and Beatty [10] estimated by colorimetry that the degree of dissociation of phosphorus pentabromide, in carbon disulphide and carbon tetrachloride, lay between 90 and 100%. Benzene solutions of phosphorus pentabromide were studied cryoscopically by Oddo and Tealdi,[11] who found that the dissociation was complete. More recently, Popov and his co-workers [12, 13] have studied phosphorus pentabromide in carbon tetrachloride cryoscopically and estimated the molar extinction coefficient of phosphorus pentabromide and deduced a value of about 50% for the degree of dissociation.

In the conductance experiments herein described, the solvent used was acetonitrile, which has very favourable dielectric properties; in addition its behaviour as a Lewis base frequently results in ion-stabilisation. It was thought that, in this solvent, phosphorus pentabromide would be dissociated ionically to a considerable degree.

Results and Discussion

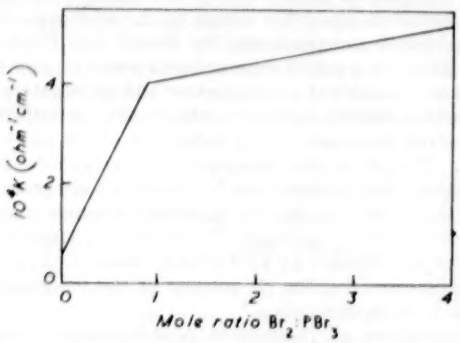
The results of conductometric titration for the system phosphorus tribromide–bromine in acetonitrile are shown in the Figure. The conductances of bromine and phosphorus tribromide in acetonitrile have been determined separately; both are virtually non-conductors in this solvent (Br_2, $\Lambda_m = 0{\cdot}22$ ohm^{-1} cm.^{2} mole^{-1}, $c_m = 0{\cdot}033$; PBr_3, $\Lambda_m = 1{\cdot}78$ ohm^{-1} cm.^{2} mole^{-1}, $c_m = 0{\cdot}025$). It is therefore evident that the reaction of bromine and phosphorus tribromide in acetonitrile is accompanied by the production of ions. The form of the

[1] Payne, *J.*, 1953, 1052.
[2] Harris and Payne, *J.*, 1956, 3038.
[3] Powell and Clark, *Nature*, 1940, **145**, 971.
[4] Van Driel and MacGillavry, *Rec. Trav. chim.*, 1943, **62**, 167.
[5] Walden, *Z. phys. Chem.*, 1903, **43**, 434.
[6] Plotnikov, *ibid.*, 1904, **48**, 230.
[7] Finkelstein, *ibid.*, 1925, **115**, 306.
[8] *Idem*, *ibid.*, 1927, **125**, 229.
[9] *Idem*, *ibid.*, 1923, **105**, 10.
[10] Kastle and Beatty, *Amer. Chem. J.*, 1899, **21**, 392.
[11] Oddo and Tealdi, *Gazzetta*, 1903, **33**, 435.
[12] Popov and Schmorr, *J. Amer. Chem. Soc.*, 1952, **74**, 4672.
[13] Popov and Skelly, *ibid.*, 1954, **76**, 3916.

graph, with its abrupt change of slope at a mole ratio of 1, indicates the presence of an ionic complex with the composition PBr_3,Br_2 (*i.e.*, phosphorus pentabromide).

Considerable interest attaches to the mole ratios 2 and 3 in view of the reported existence of hepta- and ennea-bromides of phosphorus.[14, 15] The absence of inflections in the curve at these ratios suggests that the solution does not contain any new type of ion derived from a hepta- or ennea-bromide, but is simply a solution of phosphorus pentabromide plus excess of bromine.

If phosphorus pentabromide were represented in solution by the same ions as in the solid state, PBr_4^+ and Br^-, then the conditions ('onium type cation [16] in acetonitrile solution [17]) would favour the formation of the tribromide ion on the addition of further



amounts of bromine after mole ratio 1, and this would be reflected in the graph by a break at the mole ratio corresponding to PBr_7. However the absence of an inflection on the graph beyond mole ratio 1 seems to indicate that the process

$$PBr_3 \xrightarrow{Br_2} PBr_3,Br_2 \longrightarrow PBr_4^+ + Br^- \xrightarrow{Br_2} PBr_4^+ + Br_3^-$$

is not taking place. It therefore appears reasonable to suggest that phosphorus pentabromide does not ionise in acetonitrile in the manner shown in this scheme. It is possible that the ions present are analogous to those occurring in acetonitrile solutions of phosphorus pentachloride,[1] *viz.*, PCl_4^+ and PCl_6^-, and this point has been pursued by quantitative electrolysis experiments described later.

It is concluded from the result of the conductometric titration that the equilibrium

$$PBr_3 + Br_2 \rightleftharpoons PBr_5 \rightleftharpoons \text{ions}$$

is rapidly established.

The conductances of pure phosphorus pentabromide in acetonitrile, measured at different concentrations, are shown in Table 1. The specific conductance (κ) of the solution

TABLE 1. *Conductance of phosphorus pentabromide in acetonitrile at 25°.*

c_m (mole l.$^{-1}$)	0·0152	0·0195	0·0296	0·0729
$10^4\kappa$ (ohm^{-1} cm.$^{-1}$)	2·12	2·78	3·63	5·67
Λ_m (ohm^{-1} cm.^{2} mole^{-1})	13·95	14·25	12·26	7·86

increased slightly with time ($2{\cdot}2 \times 10^{-7}$ ohm^{-1} cm.$^{-1}$ hr.$^{-1}$), and the value used to calculate the molar conductance (Λ_m) was obtained by extrapolating a plot of the specific conductance against time to $t = 0$. A conductance drift was observed by Popov and Skelly [18] with acetonitrile solutions of inter-halogen compounds.

[14] Kastle and Beatty, *Amer. Chem. J.*, 1900, **23**, 505.
[15] Biltz and Jeep, *Z. anorg. Chem.*, 1927, **162**, 32.
[16] Sidgwick, "The Chemical Elements and Their Compounds," Oxford Univ. Press, London, 1950. p. 1194.
[17] Popov and Skelly, *J. Amer. Chem. Soc.*, 1954, **76**, 5309.
[18] *Idem, ibid*, 1955, **77**, 3724.

The molar conductance of phosphorus pentabromide in acetonitrile varies (approximately) linearly with the square root of the concentration. At values of c_m less than about 0·015M, the values obtained for Λ_m were irregular and unreproducible. This is presumably due to the enhanced influence of traces of impurities at such low concentrations. The molar conductance at a given concentration varied slightly with the batch of acetonitrile, but within the same batch the values formed a consistent series. Solutions of phosphorus pentabromide in acetonitrile had a positive temperature coefficient within the range 0—25°.

It is possible that in acetonitrile phosphorus pentabromide might also undergo molecular dissociation to some extent. These conducting solutions would then also contain molecules of phosphorus tribomide and bromine. That these molecules do not contribute significantly to the conductance of the solutions has already been demonstrated.

Clearly, then, we must regard the conductance of these acetonitrile solutions as being a consequence of the electrolytic behaviour of phosphorus pentabromide. The general stability of acetonitrile as a solvent for phosphorus pentabromide is supported by the fact that cooling of such a solution yields analytically pure phosphorus pentabromide. There is no evidence for the formation of solid solvates. Phosphorus pentachloride behaves similarly in this respect.[1]

Two modes of ionisation of phosphorus pentabromide appear plausible. First, ionisation might involve the ions present in the solid state, thus :

$$PBr_5 \rightleftharpoons PBr_4^+ + Br^- \quad \ldots \quad (i)$$

On the other hand, as suggested earlier, it may be analogous to that of phosphorus pentachloride in the same solvent : [1]

$$2PBr_5 \rightleftharpoons PBr_4^+ + PBr_6^- \quad \ldots \quad (ii)$$

To determine whether one of these schemes is correct, the solution is electrolysed by a known quantity of direct current, and the changes in composition of the solution at each electrode are measured. If ΔBr = increase in g.-atoms of Br at cathode, ΔP = increase in g.-atoms of P at anode, t_+ = transport number of cation, and x = quantity of current passed (in Faradays), then for ionisation (i), provided no phosphorus or bromine is lost from the solution during electrolysis,

$$\Delta Br = x(5t_+ - 1) \qquad \Delta P = -xt_+$$

and for ionisation (ii),

$$\Delta Br = x(10t_+ - 6) \qquad \Delta P = x(1 - 2t_+)$$

Values of t_+ can thus be obtained by substitution of the observed Δ values. This was done, and it was found that a concordant set of results was obtained for t_+ when the experimental data were inserted in the equations for ionisation (ii) ($t_+ = 0{\cdot}55$, 0·54, 0·44). Phosphorus pentabromide therefore ionises in acetonitrile to yield a hexabromophosphate anion, whereas in the solid state a simple bromide ion is involved.

Preliminary experiments have shown that phosphorus pentabromide and stannic bromide form two ionic complexes, $PBr_5,SnBr_4$ and $(PBr_5)_2,SnBr_4$, stable in acetonitrile solution. There is no evidence on the nature of the ions present in these solutions, but by analogy with the phosphorus pentachloride–stannic chloride system [19] it seems probable that the 2 : 1-compound ionises to produce the ions PBr_4^+ and $SnBr_6^{2-}$. No attempt has yet been made to isolate these complexes.

Solutions of phosphorus pentabromide in nitrobenzene have been shown by Finkelstein [7] to be very poor conductors of electricity ($\Lambda_m = 0{\cdot}224$ ohm^{-1} cm.^{2} mole^{-1}; $c_m = 0{\cdot}147$); hence it is inferred that electrolytic dissociation of phosphorus pentabromide in this solvent is negligible. A cryoscopic investigation of the phosphorus tribromide–bromine–nitrobenzene system should therefore indicate the extent of molecular dissociation of phosphorus pentabromide in nitrobenzene: Freezing points were determined, first for phosphorus tribromide in nitrobenzene, and then for this solution containing added amounts of bromine.

[19] Payne, unpublished results.

The values bore a linear relationship to the mole ratio $Br_2 : PBr_3$. Thus by graphical interpolation the freezing point of the system could be obtained for integral values of the mole ratio, and thus the number of particles present in the solution at mole ratios 1, 2, and 3 could be calculated. To simplify the calculations these values were used in all subsequent calculations.

Consideration was given to the equilibria

$$PBr_3 + Br_2 \rightleftharpoons PBr_5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$PBr_3 + 2Br_2 \rightleftharpoons PBr_7 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$PBr_3 + 3Br_2 \rightleftharpoons PBr_9 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

For each of these, expressions for the association constant at mole ratios 1, 2, and 3 were derived. Substitution of the experimental results in the nine equations so obtained gave the values of association constant shown in Table 2 (the subscript preceding a symbol denotes the mole ratio, and that following the symbol denotes the equilibrium being considered).

TABLE 2. *Association constants in the system* PBr_3–Br_2–Ph·NO_2

PBr_5	PBr_7	PBr_9
${}_1K_1 = 2{\cdot}208$	${}_1K_2 = 16{\cdot}112$	${}_1K_3 = 164{\cdot}20$
${}_2K_1 = 2{\cdot}246$	${}_2K_2 = 8{\cdot}289$	${}_2K_3 = 41{\cdot}13$
${}_3K_1 = 2{\cdot}731$	${}_3K_2 = 5{\cdot}570$	${}_3K_3 = 17{\cdot}91$

From these results it is clear that the equilibrium $PBr_3 + Br_2 \rightleftharpoons PBr_5$ describes the system more closely than any other single equilibrium.

The possibility of two or more equilibria being involved simultaneously was considered, and it became clear that the experimental observations could best be interpreted by taking into account equilibria (1) and (2). The values of equilibrium constants were calculated to be :

for equilibrium (1), $K_{5\cdot7^\circ} = 2{\cdot}018$ mole^{-1} litre;

,, ,, (2), $K_{5\cdot7^\circ} = 1{\cdot}448$ mole^{-2} litre^2.

The degrees of association at the various mole-ratios are given in Table 3 and it is seen that these are relatively low. Thus it can be concluded that the degree of molecular dissociation

TABLE 3. *Degrees of association in the system* PBr_3–Br_2–Ph·NO_2, *consisting of equilibria* (1) *and* (2)

Mole-ratio $PBr_3 : Br_2$	PBr_5 equilibm.	PBr_7 equilibm.	α_1/α_2
1 : 1	${}_1\alpha_1 = 0{\cdot}1134$	${}_1\alpha_2 = 0{\cdot}005208$	${}_1\alpha_1/{}_1\alpha_2 = 21{\cdot}77$
1 : 2	${}_2\alpha_1 = 0{\cdot}2033$	${}_2\alpha_2 = 0{\cdot}01875$	${}_2\alpha_1/{}_2\alpha_2 = 10{\cdot}84$
1 : 3	${}_3\alpha_1 = 0{\cdot}2709$	${}_3\alpha_2 = 0{\cdot}03769$	${}_3\alpha_1/{}_3\alpha_2 = 7{\cdot}24$

Initial PBr_3 concentration = 0·07306M.

of phosphorus pentabromide in nitrobenzene is fairly high (*ca.* 90%).

This result indicates that solutions of phosphorus pentabromide in nitrobenzene do contain PBr_5 entities and to a smaller extent PBr_7 entities. The question of the structure of these units arises, but cannot yet be answered with certainty. The PBr_5 unit may be either a trigonal bipyramidal structure or an ion-pair. The PBr_7 unit may be regarded as a complex formed between the PBr_5 entity and a bromine molecule through the latter's donating a pair of its unbonded electrons to the phosphorus atom producing a six-co-ordinated phosphorus atom with the same electronic structure as in PBr_6^-. An ion-pair formulation, $[PBr_4^+][Br_3^-]$, is also possible for PBr_7, but it should be noted that PBr_3,Br_4 could not be recognised as an ionic complex in acetonitrile solution.

A cryoscopic investigation of the system phosphorus tribromide–bromine in carbon tetrachloride would have been valuable in view of the spectrophotometric studies of solutions of phosphorus pentabromide in this solvent,[12, 13] but this was not possible because of the low solubility of the pentabromide (or more correctly PBr_5,$2CCl_4$).

Experimental

Purification of Materials.—The purification of acetonitrile for conductance measurements has already been described,[2] and the preparation of pure nitrobenzene is given in the preceding paper. Bromine and phosphorus tribromide were purified by fractionation in a vacuum, and the pure material was stored in sealed ampoules. Phosphorus pentabromide was purified by recrystallisation (cf. Van Driel and Gerding [21]). The crude material (10 g.) was dissolved in pure nitrobenzene (50 c.c.) at 60°. A fine, white, insoluble residue remained and this was removed by filtering the solution through a sintered-glass filtration apparatus (designed to produce anhydrous conditions). The solution was cooled, and the phosphorus pentabromide appeared as fine yellow crystals which were filtered off. The crystals were washed with sodium-dried ether (100 c.c.) and stored in a ground-glass, stoppered tube kept in a desiccator (Found : Br, 92·83, 93·30; P, 7·18. Calc. for PBr_5 : Br, 92·81; P, 7·19%).

Analysis.—The solid material and solutions of phosphorus pentabromide were hydrolysed by boiling with 2N-sodium hydroxide solution. Aliquot portions of the resulting solution were then analysed separately for bromide and phosphate ion. The former was determined by Volhard's method, and the latter by precipitation as magnesium ammonium phosphate, which was ignited and weighed as pyrophosphate.

Conductometric Analysis, Conductance Measurements, Quantitative Electrolysis and Cryoscopy.—The apparatus and techniques were similar to those described in previous papers.[1, 2, 20]

Thanks are due to the Department of Scientific and Industrial Research for financial assistance to one of us (G. S. H.).

The University, Glasgow, W.1. [*Received, July 9th, 1956.*]

[20] Harris and Payne, *J.*, preceding paper.
[21] Van Driel and Gerding, *Rec. Trav. chim.*, 1941, **60**, 869.

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886. *Pteridine Studies. Part X.* Pteridines with more than One Hydroxy- or Amino-group.*

By Adrien Albert, J. H. Lister, and Christian Pedersen.

Syntheses of new di- and tri-hydroxy- (and amino-)pteridines are described, and a critical discussion of the solubilities of hydroxy- and amino-pteridines is presented. The hysteresis loop traced out by 2 : 6-dihydroxypteridine on titration with alkali (followed by back-titration) is discussed as being due to a further example of covalent hydration.

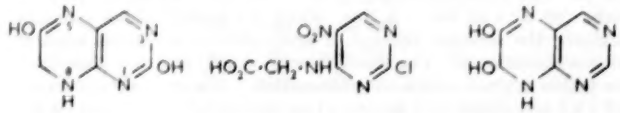
It has been shown that the insertion of a hydroxy- or an amino-group into pteridine greatly decreases the solubility in water, and the explanation has been advanced that this is due to unusually strong O–H–N and N–H–N bonds in the crystal lattice.[1] These are believed to be hydrogen bonds re-inforced by dipoles.[2] The phenomenon has been demonstrated in other heterocyclic systems.[2, 3, 4] It is known that the insolubilizing group need not be potentially tautomeric,[1] and can even be separated from the nucleus by a methylene group.[5]

The nature of such polyhydroxypteridines as have been examined [1, 6] suggests that the addition of each further hydroxy-group continues to decrease the solubility in water, and this is further explored here by the examination of the remaining polyhydroxypteridines.

* Part IX, *J.*, 1956, 3443.

[1] Albert, Brown, and Cheeseman, *J.*, 1952, 4219.
[2] Albert, in "Recent Work on naturally Occurring Nitrogen Heterocyclic Compounds," *Chem. Soc., Special Publ. No.* 3, 1955, p. 126.
[3] Fischer, *Ber.*, 1899, **32**, 498.
[4] (*a*) Albert, *Chem. and Ind.*, 1956, 252; (*b*) Albert and Brown, *J.*, 1954, 2060.
[5] Albert, *Chem. and Ind.*, 1955, 202.
[6] Albert and Brown, *J.*, 1953, 74.

The solubilities of polyamino-heterocycles have not been well explored. In the purine series, the insolubilizing effect of one amino-group is reversed when further such groups are inserted,[4] but this does not appear to be a general rule (cf. 2-amino-, 3-amino-, 2 : 6-diamino-, and 2 : 3-diamino-pyridine, whose solubilities are 1 in 1, <1, 10, and 515 respectively in water at 20°). Hence some polyaminopteridines have been synthesized and examined.



(I) (II) (III)

Hydroxypteridines.—In N-hydrochloric acid, 4 : 5-diamino-2-hydroxypyrimidine combined with ethyl glyoxylate to give 2 : 6-dihydroxypteridine, the 2 : 6-orientation of which was proved when the same substance was obtained by oxidizing 7 : 8-dihydro-2 : 6-dihydroxypteridine [7] (I), prepared from 4-carboxymethylamino-2-chloro-5-nitropyrimidine (II). When the glyoxylate condensation was done at pH 4, a mixture of 2 : 6- and 2 : 7-dihydroxypteridine was produced. This agrees with previous observations that highly acid conditions favour 6-hydroxy-orientation at the expense of the 7-position. Both isomers crystallize with one molecule of water; the 2 : 7-isomer loses this at 180° without further change, but the 2 : 6-isomer decomposes before water is lost. However, there can be no doubt that the pyrazine ring has closed in this " 2 : 6-isomer " because of its formation from (I) which is anhydrous, and because the anion absorbs at so long a wavelength.

The very large difference of 113 mμ between the long-wave ultraviolet absorption peaks of anion and neutral molecule of 2 : 6-dihydroxypteridine points to the formation of a new conjugated double bond in alkali (see Table 1). This reaction is not instantaneous. 2 : 6-Dihydroxypteridine gave two spots in paper chromatography, and each when eluted, equilibrated in acid or alkali, and re-applied to paper developed *both* original spots. 4 : 6-Dihydroxypteridine [6] and xanthopterin [8] also behave thus and, like 6-hydroxypteridine itself, give hysteresis loops on titration with alkali followed by back-titration.[9] The existing evidence suggests that the stable form of the neutral molecule (pK 9·8) of 6-hydroxypteridine is covalently hydrated, and is actually 7 : 8-dihydro-6 : 7-dihydroxypteridine [10] (III), but the stable form of the anion is anhydrous, and corresponds to a stronger acid (pK 6·7). 2 : 6-Dihydroxypteridine is too insoluble to be titrated in this way, but spectrophotometry in a series of buffers revealed a similar hysteresis loop. Thus the absorption at 412 mμ (a peak peculiar to the anion) was plotted against pH, giving two curves depending on whether the substance added to the buffers had been dissolved in water or in alkali (see Figure).

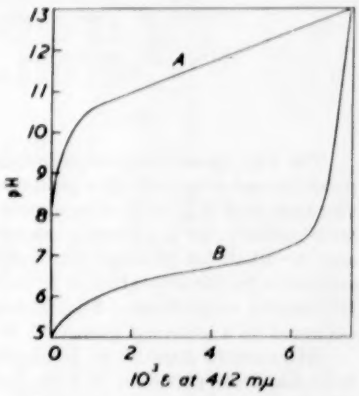
The lower curve (obtained by the rapid adjustment of an alkaline solution to lower pH values) corresponds to an acid of pK ~ 6·7 because 50% of the density (at 412 mμ) of the anionic peak persisted down to pH 6·7. The upper curve (obtained by rapid adjustment of a neutral solution to higher pH values) corresponds roughly to an acid to pH ~ 11·6. However, the upper curve does not have such a theoretically correct shape and it would appear that (as with 6-hydroxypteridine [10]) there are two monoanions as well as two neutral molecules, the anion absorbing at 412 mμ being far the more stable. Further proof that the pK of the stable neutral molecule lies above 9 came from the aqueous solubility which was identical at pH 3·7, 6·3, and 7·9 (20°). The pK of 6·7 represents an equilibrium between the stable anion and the transient neutral molecule, and is assigned to the 6- rather than the 2-hydroxy-group, because the ionization of a 2-hydroxy-group does not induce hysteresis in 2-hydroxy- or 2 : 4- or 2 : 7-di-hydroxy-pteridine. In analogy with 6-hydroxypteridine,[10] the stable neutral molecule would be 7 : 8-dihydro-2 : 6 : 7-trihydroxypteridine in water.

[7] Boon, Jones, and Ramage, *J.*, 1951, 96.
[8] Tschesche and Korte, *Chem. Ber.*, 1952, **85**, 139.
[9] Albert, Ciba Symposium on Chem. and Biol. of Pteridines, Churchill, London, 1954, p. 210.
[10] Brown and Mason, *J.*, 1956, 3443.

But the true structure seems to be yet more complex because even the stable anion (pK 6·7) gives no sign of forming a dianion even at pH 13, whereas the 2 : 7-isomer forms a dianion with pK 10·1 (as the pK of the monoanion is 5·8, the failure of the 2 : 6-isomer to produce a dianion cannot be attributed to a coulombic effect). Thus water may be covalently bound by the pyrimidine ring as well, and the stable neutral molecule would then be 3 : 4 : 7 : 8-tetrahydro-2 : 4 : 6 : 7-tetrahydroxypteridine (IV) (see below).

Condensation of 4 : 5-diaminopyrimidine with ethyl glyoxylate hemiacetal at pH 6 gives a mixture of 6- and 7-hydroxypteridine.[11] However, a method for obtaining the 6-hydroxy-isomer exclusively was described recently,[12] and it is now found that the 7-isomer is formed exclusively and in excellent yield by carrying out the condensation in boiling 2N-sodium carbonate.

The synthesis of trihydroxypteridines will now be discussed. Wieland and Liebig [13] attempted the synthesis of 2 : 4 : 6-trihydroxypteridine from 5 : 6-diamino-2 : 4-dihydroxypyrimidine and glyoxylic acid, but did not examine the product for homogeneity or orientation. By purification through the potassium salt, a product free from the 2 : 4 : 7-isomer



2 : 6-Dihydroxypteridine. Hysteresis loop caused by slowly equilibrating forms. Readings taken 60 sec. after mixing (4 cm. cells).

A, Solution in water added to buffers, whose pH's *were chosen (by trial) to give about 10% progressive change in extinction. B, Solution in 0·01N-potassium hydroxide treated similarly.*

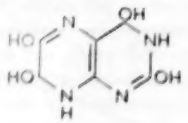
has now been obtained, and the orientation confirmed by obtaining the same substance by the action of sodium amalgam on tetrahydroxypteridine and oxidation of the product, 7 : 8-dihydro-2 : 4 : 6-trihydroxypteridine.[14] This is an established method for selectively removing a 7-hydroxy-group.[11,15]

2 : 4 : 7-Trihydroxypteridine has been obtained from its 6-carboxylic acid.[16] A direct synthesis was attempted from the reactants used to make the 2 : 4 : 6-isomer, but at pH 5 or above. The product, as in the similar synthesis of *iso*xanthopterin,[17] was an anil. This was cyclized with boiling 2N-ammonia, to 2 : 4 : 7-trihydroxypteridine which could not be obtained homogeneous. However, a satisfactory product was obtained by the alkaline hydrolysis of 4-amino-2 : 7-dihydroxypteridine, which was easily prepared from triamino-2-hydroxypyrimidine and ethyl glyoxylate.

As 4 : 6 : 7-trihydroxypteridine is known,[6] only the 2 : 6 : 7-isomer remained to be made. By heating 4 : 5-diamino-2-hydroxypyrimidine (dry or in water) with oxalic acid or methyl oxalate, also by oxidizing 2 : 6- or 2 : 7-dihydroxypteridine, we obtained a substance which, after recrystallization six times from water (the only suitable solvent), gave elementary analyses consonant with the hemihydrate of the required substance. Nevertheless, it

[11] Albert, Brown, and Cheeseman, *J.*, 1952, 1620.
[12] Albert, *J.*, 1955, 2690.
[13] Wieland and Liebig, *Annalen*, 1944, **555**, 146.
[14] Boon and Leigh, B.P. 677,342/1950.
[15] Totter, *J. Biol. Chem.*, 1944, **154**, 105.
[16] Tschesche and Korte, *Chem. Ber.*, 1951, **84**, 801.
[17] Albert and Wood, *J. Appl. Chem.*, 1953, **3**, 521.

titrated with alkali as a mixture of substances with p*K*'s 6·4 and 3·5. When it was first dissolved in alkali and back-titrated the same p*K*'s were obtained (evidence that it was not hydrolysed by hydrogen ions, the 0·001-M-solution being acidic). No hysteresis was observed during these titrations. In chromatography (in 3% aqueous ammonium chloride) it gave two spots, one fluorescing blue (R_F 0·50) and a dark, absorbing spot (R_F 0·75) (both in light of λ 254 mμ). No known di-, tri-, or tetra-hydroxypteridine gives a dark spot. When the dried paper was kept in the dark for a day, the dark spot changed to a blue fluorescence even when there had been no prior irradiation. However, when the paper was kept moist, the change was exceedingly slow. Separate elution with water of both spots (whether in the dark or the fluorescent condition) and reapplication to paper produced from each eluate a blue fluorescent spot at R_F 0·50, and a dark spot at R_F 0·75 which fluoresced after dry storage. Thus the evidence suggests that the material produced is a mixture of two components which freely enter into equilibrium with one another. The chromatographic behaviour was the same whether the substance was applied to paper in acid, neutral, or alkaline solution.



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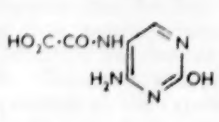

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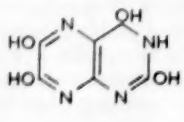


(VI)

The two most likely explanations of these phenomena are that 2 : 6 : 7-trihydroxypteridine can exist only in equilibrium with (i) its precursor 4-amino-2-hydroxypyrimid-5-yloxamic acid (V), or (ii) a covalently hydrated form, *e.g.*, (VI). The first explanation may seem unlikely, for the three isomeric trihydroxypteridines are stable, unchanged by boiling acid or alkali (as also are tetra- and the six di-hydroxypteridines [1]). Nevertheless it is supported by the formation of 4 : 5-diamino-2-hydroxypyrimidine in boiling acid. Against the second explanation, 6-hydroxypteridines are not hydrated when the 7-position is occupied by a hydroxyl group.[11] No conclusion can yet be reached.

Attempts to make 2 : 6 : 7-trihydroxypteridine by the action of nitrous acid on 2-amino-6 : 7-dihydroxypteridine led to profound decomposition. An improved synthesis of tetrahydroxypteridine is described.

Aminopteridines.—All the monoaminopteridines are known,[19] but only the 2 : 4- and 4 : 7-diaminopteridines.[20,1] The 4 : 6-isomer has now been obtained by the action of ammonia on the chlorination product of 4 : 6-dihydroxypteridine. 2 : 6-, 2 : 7-, and 6 : 7-Dihydroxypteridines gave no chloro-compounds with phosphorus halides, and were destroyed if conditions were severe. 6 : 7-Diaminopteridine could not be obtained by the action of cyanogen or dithio-oxamide on 4 : 5-diaminopyrimidine. The spectra of the neutral molecules of 4 : 6- and 4 : 7-diaminopteridines are almost identical with those of the dianions of the corresponding dihydroxypteridines,[6] a relation established for the mono-substituted analogues.[19]

The only known triaminopteridine is the 2 : 4 : 7-isomer, obtainable in very small yield by heating the 6-carboxylic acid.[20b] It has now been obtained in good yield from 2 : 4 : 7-trihydroxypteridine, *via* the trichloropteridine. The 4 : 6 : 7-isomer was prepared similarly.

Solubility.—Table 2 lists the solubilities of all possible hydroxypteridines (except 2 : 6 : 7-trihydroxypteridine which is not yet known beyond doubt, see above). Only three substances in Table 2 show hysteresis during titration (6-hydroxy- and 2 : 6- and 4 : 6-dihydroxy-pteridine), and two of these are abnormally insoluble. The averages (these two being set aside) show that addition of each hydroxy-group to pteridine further increases insolubility. The figures are compatible with the hypothesis advanced earlier that " 6-hydroxypteridine " may be in reality covalently hydrated to the dihydroxypteridine (III),

[18] Bertho and Bentler, *Annalen*, 1950, **570**, 127; Schöpf, Reichert, and Riefstahl, *ibid.*, 1941, **548**, 82.
[19] Albert, Brown, and Wood, *J.*, 1954, 3832.
[20] (*a*) Mallette, Taylor, and Cain, *J. Amer. Chem. Soc.*, 1947, **69**, 1814; (*b*) Osdene and Timmis, *J.*, 1955, 2036.

Table 1. Physical properties of pteridines.

Pteridine	Ionization [a] (H_2O; 20°) pK_a	spread ±	concn. M	Solubility in H_2O 20° 1 in	100°	Spectroscopy in water [f] $\lambda_{max.}$ (mμ)	log ε	pH
2 : 6-Dihydroxy [g]	—	—	—	110,000 [d]	4500	235, 299	4·22, 3·79	3·9 or 7·8
monoanion (anhyd.)	6·7 [d]	— [h]	0·00002	—	—	225, 246, 412	4·41, 4·23, 3·87	13
monoanion (hydrated [a])	11·6 [d]	— [h]	0·00002	—	—	—	—	—
2 : 7-Dihydroxy	—	—	—	1,400	100	258, 328	3·99, 4·11	3·6
monoanion	5·83	0·02	0·005	—	—	282, 343, 359	3·54, 4·42, 4·43	7·9
dianion	10·07	0·06	0·005	—	—	224, 271, 343, 353	4·50, 3·78, 4·25, 4·20	12
2 : 4 : 6-Trihydroxy	—	—	—	7,400	400	223, 248, 300, 364	4·04, 3·99, 3·16, 3·73	3·5
monoanion	5·73	0·03	0·0007	—	—	222, 265, 379	4·15, 4·05, 3·83	7·5
dianion	9·41	0·02	0·0007	—	—	234, 274, 394	4·15, 3·07, 3·80	13 [h]
2 : 4 : 7-Trihydroxy	—	—	—	12,000 [d]	1400	—	—	—
monoanion	3·61	0·02	0·0005	—	—	225, 248, 275, 335	4·42, 3·92, 3·86, 4·13	13 [h]
2 : 4 : 6 : 7-Tetrahydroxy	—	—	—	58,000 [d]	7000	233, 292, 346	4·27, 3·88, 4·11	13 [h,i]
4 : 6-Diamino	—	—	—	24,000 [d]	940	263, 375	4·18, 3·81	6·7
monocation	4·37 [d]	0·03	0·0002	—	—	254, 284, 376	4·09, 3·87, 3·90	2·4
4 : 7-Diamino [g]	—	—	—	5,000	300	241, 339	4·38, 4·05	7·0
monocation	4·97 [j]	0·03	0·001	—	—	233, 257, 284, 343	4·24, 4·22, 3·69, 4·14	3·0
2 : 4 : 7-Triamino	—	—	—	4,500	200	227, 257, 350	4·54, 4·13, 4·17	8·5
monocation	6·30	0·04	0·001	—	—	255, 275, 342	4·16, 3·84, 4·28	4·3
4 : 6 : 7-Triamino	—	—	—	12,500 [d]	450	227, 256, 284, 345	4·33, 4·17, 3·63, 4·11	8·5
monocation	5·57	0·02	0·001	—	—	224, 245, 353	4·20, 4·21, 4·26	3·6
2 : 4 : 6 : 7-Tetramino [b]	6·86 [d,e]	0·03	0·0001	13,000 [d]	—	— [k]	—	—
2-Amino-6 : 7-dihydroxy	—	—	—	—	—	244, 348	4·26, 4·09	13 [h]
4-Amino-2 : 7-dihydroxy	—	—	—	—	—	223, 256, 344	4·42, 4·04, 4·12	13 [h]

[a] Covalently monohydrated. [b] We thank Dr. E. C. Taylor of Princeton University for this substance, and understand that he is reporting on its spectroscopy. [c] Determined potentiometrically except where otherwise shown (for details see Albert and Phillips, *J.*, 1956, 1294). [d] Determined spectrophotometrically. [e] We thank Mr. G. Timmis for this substance. [f] Cf. 2 : 4-diaminopteridine, 5·32. [g] Monocation: analytical wave-length was 265 mμ. [h] Approx., see Fig. [i] Hilger "Uvispek" photoelectric spectrophotometer (1 cm. cells). [k] Polyanion. [l] This replaces earlier values on material now known to be impure.

and "2 : 6-dihydroxypteridine" to the tetrahydroxypteridine (IV). This argument, which ignores steric factors, must not be taken too far, but suggests that equilibrium does not favour the hydrate of 4 : 6-dihydroxypteridine.

The addition of one primary amino-group to pteridine greatly decreases solubility (all four monoaminopteridines [1,19] fall in the range 1 in 1400—1500); for 2 : 4-, 4 : 6-, and 4 : 7-diaminopteridines solubilities are 1 in 3000, 24,000, and 5000 respectively (average 11,000); for the two triaminopteridines 1 in 4500 and 12,500; and for tetra-aminopteridine 1 in 13,000. Thus, although there are not so many data as for the hydroxypteridines, it is seen that one primary amino-group has a marked insolubilising effect which, unlike the case for hydroxypteridines, is only moderately intensified by further additions of the same group.

TABLE 2. *Solubilities of hydroxypteridines in water at 20°.*

	1 in		1 in		1 in
Unsubstituted	7	2 : 4-Dihydroxy	800	2 : 4 : 6-Trihydroxy ...	7400
		2 : 6-Dihydroxy	110,000	2 : 4 : 7-Trihydroxy ...	12,000
2-Hydroxy	600	2 : 7-Dihydroxy	1400	4 : 6 : 7-Trihydroxy ...	27,000
4-Hydroxy	200	4 : 6-Dihydroxy	5500	Average	15,000
6-Hydroxy	3500	4 : 7-Dihydroxy	4000	Tetrahydroxy	58,000
7-Hydroxy	900	6 : 7-Dihydroxy	3000		
Average 400 (omitting 6-hydroxy)		Average 3000 (omitting 2 : 6-dihydroxy)			

EXPERIMENTAL

Microanalyses were by Mr. P. R. W. Baker, Beckenham. The yields refer to the stage at which substances became chromatographically homogeneous (on paper), 3% aqueous ammonium chloride or butanol–5N-acetic acid (7 : 3) being eluants. Substances were dried at 120° unless otherwise specified.

2 : 6-*Dihydroxypteridine*.—(*a*) 4 : 5-Diamino-2-hydroxypyrimidine [21] (1 g.) in N-hydrochloric acid (30 ml.) was refluxed with ethyl glyoxylate hemiacetal [22] (2 g.) for 30 min., cooled and neutralized, giving 80% of 2 : 6-*dihydroxypteridine monohydrate*. It was boiled with 50 parts of water (rejected) and recrystallized from 100 parts of boiling N-sulphuric acid in which it is far more soluble than in water but from which it is deposited uncombined. From 5000 parts of water it formed colourless crystals, decomp. >250° (Found, for material dried at 150°/0·01 mm.: C, 39·6; H, 3·25; N, 30·4. $C_6H_4O_2N_4,H_2O$ requires C, 39·6; H, 3·3; N, 30·8%). 2 : 6-Dihydroxypteridine was unchanged when shaken in 0·1N-sodium hydroxide or 2N-ammonia in air for 11 hr. The sodium and potassium salts are highly soluble in water to yellow solutions with an intense green fluorescence, which fades in daylight, but are stable in the dark at 20°.

(*b*) Potassium permanganate (0·7 g.) in water (50 ml.) was added dropwise to a stirred solution of 7 : 8-dihydro-2 : 6-dihydroxypteridine [7] (1 g.) in 0·2N-sodium hydroxide (90 ml.). After 30 minutes' further stirring, the mixture was filtered and adjusted to pH 5, giving 40% of 2 : 6-dihydroxypteridine monohydrate, identical with the above on chromatography in three solvents.

2 : 7-*Dihydroxypteridine*.—Ethyl glyoxylate hemiacetal (1·2 g., 1 equiv.) was added to 4 : 5-diamino-2-hydroxypyrimidine (1·25 g., 0·01 mole) in water (25 ml.) at 50°. The mixture was set aside at 20° for 24 hr. (initial and final pH 4). The precipitate (1·63 g.) was refluxed with 70 parts of water. The filtrate deposited 45% of 2 : 7-dihydroxypteridine, purified as the *sodium salt* by recrystallization from 2 equivs. of boiling N-sodium hydroxide. The pale crystals were washed with alcohol (Found, for material dried at 110°/0·01 mm.: C, 29·75; H, 2·5; N, 22·8; loss at 150°, 15·3. $C_6H_2O_2N_4Na_2,2H_2O$ requires C, 29·5; H, 2·5; N, 22·95; loss, 14·8%). This salt was dissolved in boiling water (no fluorescence), adjusted to pH 4, giving 2 : 7-*dihydroxypteridine* which forms colourless crystals from 100 parts of boiling water (Found, for material dried at 110°/0·01 mm.: C, 39·6; H, 3·2; N, 30·7; loss at 180°, 10·0. $C_6H_4O_2N_4,H_2O$ requires C, 39·6; H, 3·3; N, 30·8; loss, 9·9%). It was unchanged after 1 hr. at 175° (chromatographic tests) but became brown slowly at 275°.

That part of the initial precipitate which was sparingly soluble in water was again boiled with 70 parts of water (discarded), giving 45% of 2 : 6-dihydroxypteridine monohydrate,

[21] Johns, *Amer. Chem. J.*, 1911, **45**, 79; modified by Brown, *J. Appl. Chem.*, 1957, in the press.
[22] Rigby, *J.*, 1950, 1912.

identical with material described above. A condensation in phosphate buffer (pH 7) gave 65% of the 2 : 7- and 25% of the 2 : 6-isomer.

7-Hydroxypteridine (*Recommended Synthesis*).—4 : 5-Diaminopyrimidine (1·1 g., 0·01 mole) in 2N-sodium carbonate (10 ml.) was refluxed with ethyl glyoxylate hemiacetal (2·2 g., 50% excess) in a boiling-water bath for 1 hr. (final pH 9·5). The mixture was cooled and set aside at 20° for an hour. The sodium salt was filtered off, dissolved in boiling water (17 ml.) containing N-sodium hydroxide (0·5 ml.), and brought to pH 2·5 with 5N-sulphuric acid, whilst hot. The 7-hydroxypteridine [11] (77%) recrystallized from 76 parts of water.

2 : 4 : 6-*Trihydroxypteridine*.—To 5 : 6-diamino-2 : 4-dihydroxypyrimidine hemisulphate (6 g.), dissolved in 78% w/w sulphuric acid (72 ml.) at 90°, was added ethyl glyoxylate hemiacetal (6·6 g.). After 2 min. at 90°, water (300 ml.) was added and the mixture refrigerated. The crystals and potassium carbonate (8·5 g.) were dissolved in boiling water (100 ml.). The potassium salt was filtered from the chilled solution, dissolved in boiling water, brought to pH 4 with citric acid, and recrystallized from water, giving yellow 2 : 4 : 6-trihydroxypteridine (50%), decomp. 360—380° (Found : C, 39·8; H, 2·4; N, 31·3. Calc. for $C_6H_4O_3N_4$: C, 40·0; H, 2·2; N, 31·1%). A colourless modification was obtained by running a solution in 2N-ammonia through alumina, and acidifying, but this reverted on recrystallization.

Powdered sodium amalgam (4%; 20 g.) was added during 10 min. to finely divided tetrahydroxypteridine (1 g.; see below) suspended in water (15 ml.; under nitrogen). After 20 min., water (25 ml.) was added and warmed until a clear solution could be decanted from the mercury (under nitrogen). The supernatant liquid was acidified to pH 4 and cooled and the precipitate of 7 : 8-dihydro-2 : 4 : 6-trihydroxypteridine (0·9 g.) filtered off and found to be homogeneous. It has been prepared in another way.[14] Oxidation with potassium permanganate [11] gave 0·25 g. of 2 : 4 : 6-trihydroxypteridine.

2 : 4 : 7-*Trihydroxypteridine*.—Triamino-2-hydroxypyrimidine sulphate [23] (4 g.) and sodium acetate (20 g.) in acetic acid (20 ml.) and water (400 ml.) were refluxed with ethyl glyoxylate hemiacetal (4 g.) for 1 hr. The semicolloidal precipitate was dissolved in N-sodium hydroxide (with minimal heating) and poured into excess of boiling 2N-hydrochloric acid. The precipitate, boiled with water, gave 70% of 4-*amino*-2 : 7-*dihydroxypteridine* which is far less soluble in water than 2 : 4 : 7-trihydroxypteridine (Found, for material dried at 110°/0·1 mm. : C, 40·3; H, 2·7; N, 39·25. $C_6H_5O_2N_5$ requires C, 40·2; H, 2·8; N, 39·1%).

This amine (1 g.) was refluxed for 5 hr. with 6N-sodium hydroxide (20 ml.). Next day the sodium salt was filtered off, dissolved in boiling water (40 ml.), and acidified with acetic acid. The precipitate was purified as the potassium salt from 0·7N-potassium carbonate solution. Final recrystallization from water gave colourless crystals (75% calc. on amine) of 2 : 4 : 7-trihydroxypteridine (Found : C, 40·1; H, 2·6; N, 30·9%).

Attempted Preparation of 2 : 6 : 7-*Trihydroxypteridine*.—(*a*) 4 : 5-Diamino-2-hydroxypyrimidine [21] (1 g.), methyl oxalate (2 g.), and water (25 ml.) were heated under reflux in boiling water for 100 min. The solution became clear within 10 min., after which crystals were deposited (95% yield). These were repeatedly recrystallized from 1200 parts of water giving pale yellow crystals (dried over P_2O_5 at 20°) (Found : C, 36·8; H, 3·1; N, 28·95; loss at 200°, 4·3. $C_6H_4O_3N_4,H_2O$ requires C, 36·4; H, 3·0; N, 28·3; H_2O, 9·1%). Specimens dried at 20° and 200° were chromatographically identical. Boiling with N-sulphuric acid gave a little 4 : 5-diamino-2-hydroxypyrimidine.

(*b*) 4 : 5-Diamino-2-hydroxypyrimidine (4 g.) and oxalic acid dihydrate (30 g.) were intimately mixed, heated in a wide-mouthed flask to 165° during 30 min. and maintained there for 2 hr. The product was dissolved in alkali, then acidified to pH 4. The solid was recrystallized four times from water and dried (P_2O_5 at 120°) (Found : C, 37·7; H, 2·9; N, 29·5. $C_6H_4O_3N_4,0·5H_2O$ requires C, 38·1; H, 2·7; N, 29·6%). The products from both reactions are identical.

(*c*) A solution of 2 : 6-dihydroxypteridine monohydrate (0·47 g.) in 5N-sulphuric acid (12 ml.) and 30% hydrogen peroxide (8 ml.) was set aside for 3 days. The precipitate (78%) was identical with the above.

(*d*) 2 : 7-Dihydroxypteridine (0·5 g.) in cold nitric acid (*d* 1·5; 1·5 ml.) was set aside for a day. The deposit was boiled with water (12 ml.) and adjusted to pH 4 with sodium citrate and hydroxide. The precipitate (28%) was identical with the above.

2-*Amino*-6 : 7-*dihydroxypteridine*.—The following is an improvement on the fusion process.[24]

[23] Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3112.
[24] Wieland, Tartter, and Purrmann, *Annalen*, 1940, **545**, 209.

2 : 4 : 5-Triaminopyrimidine[25] (0·5 g.) and oxalic acid dihydrate (1 g.) were refluxed in water (12 ml.) for 90 min. The precipitate was collected next day and boiled with water (40 ml., rejected), taken up in N-sodium hydroxide, brought to pH 4 with acetic acid, and centrifuged. This sequence was repeated twice, and the product (0·4 g.) washed with alcohol, and ether (Found, for material dried at 130°/0·01 mm. : C, 40·0; H, 2·9; N, 38·8. Calc. for $C_6H_5O_2N_5$: C, 40·2; H, 2·8; N, 39·1%).

2 : 4 : 6 : 7-*Tetrahydroxypteridine*.—Existing methods, which use oxalic acid,[12] gave poor yields and the product was hard to purify. The following was satisfactory : 4 : 5-Diamino-2 : 6-dihydroxypyrimidine (8 g.), diethyl oxalate (16 ml.), and dried ethylene glycol (200 ml.) were refluxed for 2 hr., then cooled to 100°, and water (400 ml.) was added. The precipitate was purified as the potassium salt from 0·5N-potassium carbonate. This salt was dissolved in water and acidified, and the precipitated tetrahydroxypteridine (45%) boiled repeatedly with water (Found, for material dried at 140°/0·01 mm. : C, 36·6; H, 2·05; N, 28·4. Calc. for $C_6H_4O_4N_4$: C, 36·7; H, 2·05; N, 28·6%).

4 : 6-*Diaminopteridine*.—Finely divided 4 : 6-dihydroxypteridine[6] (1 g.) and phosphorus pentachloride (8 g., in phosphoryl chloride, 40 ml.) were refluxed at 135° for 4 hr. Excess of solvent was removed *in vacuo* at 100°, and ice added to the residue. The resulting solution was adjusted to, and held at, pH 7 with 10N-sodium hydroxide. The solid was filtered off, and the filtrate extracted with chloroform (4 × 30 ml.). The solid was extracted separately to avoid an emulsion. The combined extracts were dried (Na_2SO_4) and evaporated below 35°. As the residue (0·5 g.) slowly polymerized on attempted purification, it (0·35 g.) was heated with aqueous ammonia (*d* 0·88; 10 ml.) at 140° for 4 hr., then cooled. The precipitate, dissolved in water (120 ml.) and concentrated, gave yellow crystals (0·1 g.) of 4 : 6-*diaminopteridine* (Found, for material dried at 130° : C, 44·4; H, 3·7; N, 51·6. $C_6H_6N_6$ requires C, 44·4; H, 3·7; N, 51·8%).

2 : 4 : 7-*Triaminopteridine*.—2 : 4 : 7-Trihydroxypteridine (2 g.) and phosphorus pentachloride (10 g.) in phosphoryl chloride (100 ml.), treated similarly, gave a residue that was recrystallized from ether (by concentration), giving pale needles (77%) of 2 : 4 : 7-*trichloropteridine*, m. p. 133° (Found : C, 30·85; H, 0·8; N, 23·9; Cl, 44·8. $C_6HN_4Cl_3$ requires C, 30·6; H, 0·4; N, 23·8; Cl, 45·2%).

The trichloropteridine (1 g.) and ammonia (*d* 0·88; 10 ml.) were treated as above. The precipitate was crystallized from 0·3N-ammonia (180 ml.), giving 50% of yellow 2 : 4 : 7-triaminopteridine, not melting at 250° (Found, for material dried at 110° : C, 36·6; H, 4·2; N, 49·2. Calc. for $C_6H_7N_7,H_2O$: C, 36·9; H, 4·65; N, 50·25. Found, for material dried at 150°/0·01 mm. : C, 41·1; H, 3·5; N, 54·7. Calc. for $C_6H_7N_7$: C, 40·7; H, 4·0; N, 55·3%). It was chromatographically identical, in the two solvents, with a specimen synthesized by the older method.[26b]

4 : 6 : 7-*Triaminopteridine*.—4 : 6 : 7-Trihydroxypteridine[6] (1 g.), treated similarly, gave yellow-brown needles of 4 : 6 : 7-*trichloropteridine* (23%), m. p. 179—181°, loss occurring through emulsification (Found : C, 30·8; H, 0·4; N, 24·0; Cl, 45·2%). It was aminated as above. The product, extracted with boiling water (210 ml.; then concentrated) gave pale crystals (0·2 g.) of 4 : 6 : 7-*triaminopteridine* (Found, for material dried at 150° : C, 41·0; H, 3·7; N, 54·5%).

We thank Drs. D. J. Brown and S. F. Mason for helpful discussions, Dr. Brown for kindly providing pyrimidine intermediates, and Mr. E. P. Serjeant for the ionization constants and spectroscopy.

Department of Medical Chemistry, Australian National University, Canberra, Australia. [*Received, June 27th*, 1956.]

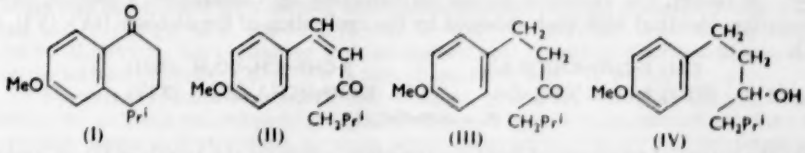
[25] Albert, Brown, and Cheeseman, *J.*, 1951, 474.

887. *Synthesis of Polycyclic Compounds. Part VI.* The Preparation of 1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxo-4-isopropylnaphthalene and Related Compounds.*

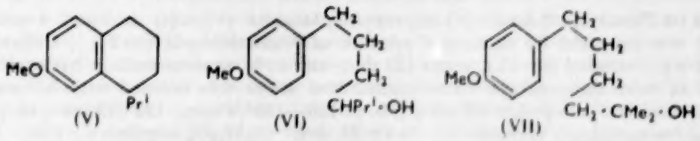
By J. C. Bardhan and D. N. Mukherji.

The isomeric alcohols (IV), (VI), and (VII), on cyclodehydration [1] with 85% phosphoric acid, afford mainly 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-*iso*propylnaphthalene, since on reduction with lithium and ethanol in liquid ammonia [2] this is converted into 2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-octahydro-2-oxo-8-*iso*propylnaphthalene. On oxidation with chromic acid the former product gives a good yield of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-1-oxo-4-*iso*propylnaphthalene, also prepared by the ring closure of 4-*m*-methoxyphenyl-5-methylhexanoic acid which has been synthesised from *m*-methoxybenzaldehyde.

In connection with another investigation we required a supply of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-1-oxo-4-*iso*propylnaphthalene (I), and the present paper reports a satisfactory preparation of it in moderate quantities.



*iso*Butyl 4-methoxystyryl ketone (II), prepared by the condensation of *p*-anisaldehyde with *iso*butyl methyl ketone in presence of alkali, on hydrogenation over W-7 Raney nickel [3] gave *iso*butyl *p*-methoxyphenethyl ketone (III), and this on further reduction with lithium aluminium hydride gave an excellent yield of 1-*p*-methoxyphenyl-5-methylhexan-3-ol (IV), which was smoothly cyclised by hot 85% phosphoric acid to 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-*iso*propylnaphthalene (V). The same hydrocarbon was obtained analogously in an inferior overall yield from the isomeric alcohols [1] (VI) and (VII).



The structure of the liquid hydrocarbon (V) follows from its reduction by lithium and ethanol in liquid ammonia [2] to the enol-ether (VIII), which on hydrolysis with ethanolic hydrochloric acid furnishes 2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-octahydro-2-oxo-8-*iso*propylnaphthalene (IX). The presence of a conjugated system in this octalone was indicated by its ultraviolet light absorption [4a] and that of its semicarbazone,[4b] and was confirmed by an unequivocal synthesis involving the coupling of 2-hydroxymethylene-6-*iso*propyl*cyclo*hexanone (X) with 4-diethylaminobutan-2-one methiodide according to known procedure.[5]

On oxidation with chromic acid the methoxy*iso*propyltetralin (V) furnishes a good yield

* Part V, *J.*, 1956, 1809.

[1] Roblin, Davidson, and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 151, and other papers.

[2] (*a*) Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5363; Birch, *J.*, 1944, **434**; (*b*) Birch, *J.*, 1946, 597.

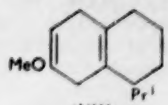
[3] *Org. Synth.*, 1949, **29**, 28; Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 697.

[4] (*a*) Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; (*b*) Evans and Gillam, *J.*, 1941, 815; 1943, 565.

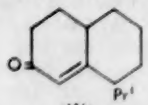
[5] Shunk and Wilds, *J. Amer. Chem. Soc.*, 1949, **71**, 3948; 1950, **72**, 2392; Woodward, Sondheimer, Taub, Heusler, and McLamore, *ibid.*, 1952, **74**, 4223.

of a ketone (semicarbazone, 2 : 4-dinitrophenylhydrazone, and piperonylidene derivative) which is regarded as (I), since several instances of such selective oxidation [6] are on record. Nevertheless, it seemed desirable to prove structure (I) by a more obvious synthesis. Derivatives of tetrahydronaphthalene such as this are, however, peculiarly difficult to prepare [7] but after several unsuccessful attempts we devised the following method.

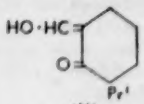
m-Methoxybenzaldehyde and *iso*propylmagnesium bromide gave 1-*m*-methoxyphenyl-2-methylpropan-1-ol which was converted into the bromide in the usual way, and then treated with ethyl sodiomalonate, affording the ester (XI). Hydrolysis and elimination of carbon dioxide gave the acid (XII). Reduction of the corresponding ethyl ester by Bouveault's method afforded the alcohol (XIII), which was successively converted through



(VIII)



(IX)



(X)

the bromide and nitrile into the acid (XIV). Ring closure with phosphoric oxide dissolved in orthophosphoric acid [8] then gave the tetralone (I), identical with the product described above. Moreover, the synthetic ketone on reduction by Clemmensen's method gave a hydrocarbon identical with that obtained by the cyclisation of the alcohols (IV), (VI), and (VII).

(XI) R·CHPr^i·CH(CO$_2$Et)$_2$ R·CHPr^i·CH$_2$·CO$_2$H (XII)

(XIII) R·CHPr^i·[CH$_2$]$_2$·OH R·CHPr^i·[CH$_2$]$_2$·CO$_2$H (XIV)

(R = *m*-MeO·C$_6$H$_4$)

By the action of an excess of methylmagnesium iodide on the tetralone (I) an unstable alcohol was obtained which when heated with potassium hydrogen sulphate yielded 3 : 4-dihydro-6-methoxy-1-methyl-4-*iso*propylnaphthalene, hydrogenated over palladium to 1 : 2 : 3 : 4-tetrahydro-6-methoxy-1-methyl-4-*iso*propylnaphthalene. This was readily reduced by lithium and ethanol in liquid ammonia [2] to 1 : 2 : 3 : 4 : 5 : 8-hexahydro-6-methoxy-1-methyl-4-*iso*propylnaphthalene.

Experimental

1 : 2 : 3 : 4-*Tetrahydro-7-methoxy-1-isopropylnaphthalene* (V).—(a) *isoButyl 4-methoxystyryl ketone* (II) was prepared by shaking a mixture of *p*-anisaldehyde (30·2 g.), *iso*butyl methyl ketone (22·2 g.), ethanol (85 ml.), water (29 ml.), and 10% aqueous sodium hydroxide (22 ml.) for 15 hr. at room temperature. The unsaturated *ketone* was isolated with benzene and on distillation formed a pale yellow oil (43 g.), b. p. 168—169°/4 mm., 192°/12 mm., m. p. 46—47° (from aqueous methanol) (Found : C, 76·4; H, 8·6. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%).

isoButyl p-methoxyphenethyl ketone (III). The ketone (II) (72 g.) in ethanol (80 ml.) was shaken with W-7 Raney nickel catalyst [9] (6 g.) in hydrogen at the room temperature; the calculated amount (8·1 l.) was absorbed in 2·5 hr. After removal of catalyst and solvent the *ketone* distilled as a colourless liquid (71 g.), b. p. 165—167°/11 mm. (Found : C, 76·3; H, 9·3. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%). The *semicarbazone* formed prisms, m. p. 113° (from ethanol) (Found : C, 65·1; H, 8·1. $C_{15}H_{23}O_2N_3$ requires C, 65·0; H, 8·3%).

1-p-*Methoxyphenyl-5-methylhexan-3-ol* (IV). The foregoing ketone (44 g.) in ether (120 ml.) was introduced during 45 min. into a stirred solution of lithium aluminium hydride (4 g.) in ether (50 ml.) at room temperature. As soon as the vigorous reaction was over, the mixture was gently refluxed for 0·5 hr., cooled in ice, and treated with water (10 ml.), followed by dilute sulphuric acid. The ethereal layer was separated and the aqueous solution repeatedly extracted with ether. The combined ether solutions were washed with water, dried (Na_2SO_4),

[6] Goertz, Diss., Berlin, 1924, p. 17; Burnop, Elliot, and Linstead, *J.*, 1940, 731; Martin and Robinson, *J.*, 1943, 493; Johnson, Anderson, and Shelberg, *J. Amer. Chem. Soc.*, 1944, **66**, 219; Schwenk and Papa, *ibid.*, 1945, **67**, 1432; Stork, *ibid.*, 1947, **69**, 579.

[7] Cf. Cocker, Cross, Edward, Jenkinson, and McCormick, *J.*, 1953, 2358.

[8] Koebner and Robinson, *J.*, 1938, 1995; Birch, Jaeger, and Robinson, *J.*, 1945, 582; Bachmann and Horton, *J. Amer. Chem. Soc.*, 1947, **69**, 58; Gilmore and Horton, *ibid.*, 1951, **73**, 1411.

and distilled, the *alcohol* (IV) (42·5 g.) being obtained as a colourless, somewhat viscous liquid, b. p. 173°/12 mm. (Found: C, 75·8; H, 9·8. $C_{14}H_{22}O_2$ requires C, 75·7; H, 9·9%). The alcohol (25 g.) and phosphoric acid (50 ml.; *d* 1·7) were heated in an oil-bath at 175—180° under reflux with stirring for 12 hr. After cooling, water was added and the oil extracted with ether. The ethereal solution was washed with a solution of sodium carbonate and with water, dried ($CaCl_2$), and evaporated. The residual liquid (22 g.) was heated in an oil-bath at 150—160° with sodium (1 g.) for 5 hr. and then distilled. 1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-1-iso*propyl*-*naphthalene* (V) formed a colourless oil (19·8 g.), b. p. 145°/13 mm., $n_D^{19\cdot5}$ 1·5330 (Found: C, 82·3; H, 9·7. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%).

(b) 3-p-*Methoxyphenylpropyl alcohol*.[9] Ethyl 4-methoxycinnamate [10] (b. p. 162—165°/4 mm.) (40 g.) was reduced with sodium (40 g.) and calcium-dried ethanol (350 ml.). The resulting alcohol (21 g.) had b. p. 133—134°/4 mm. (Found: C, 72·1; H, 8·3. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·4%).

The alcohol (20 g.), dimethylaniline (28 ml.), and dry chloroform (28 ml.) were cooled in ice and gradually mixed with thionyl chloride (22·5 g.) in dry chloroform (28 ml.), and the mixture was heated on the steam-bath for 45 min. The *chloride* (20 g.) boiled constantly at 130°/5 mm. (Found: Cl, 19·5. $C_{10}H_{13}OCl$ requires Cl, 19·2%).

*iso*Butyraldehyde (5 g.) in ether (10 ml.) was added dropwise with constant shaking to an ice-cold ethereal solution of the Grignard reagent from 3-*p*-methoxyphenylpropyl chloride (11 g.), magnesium (1·5 g.), and dry ether (30 ml.). After 12 hr. at room temperature the mixture was decomposed with ice and ammonium chloride, giving 6-p-*methoxyphenyl*-2-*methylhexan*-3-*ol* (VI) (8 g.), b. p. 156—158°/5 mm. (Found: C, 75·4; H, 10·1. $C_{14}H_{22}O_2$ requires C, 75·7; H, 9·9%). On cyclisation with phosphoric acid (8 ml.) as described above, it (4 g.) gave the tetralin (V) (2·5 g.), b. p. 132°/4 mm. (Found: C, 82·1; H, 9·7%).

(c) δ-*p*-Methoxyphenyl-δ-oxovaleric acid [11] (50 g.), potassium hydroxide (35 g.), hydrazine hydrate (25 ml.), and trimethylene glycol (250 ml.) were heated under reflux [12] provided with a continuous water-separator until no more water collected (1·5 hr.). The temperature was allowed to rise to 195° and refluxing continued for 4 hr. more. The crude 5-*p*-methoxyphenylpentanoic acid [13] (46 g.), isolated in the usual way, was converted into the *ethyl ester*, b. p. 159°/4 mm. (Found: C, 71·1; H, 8·6. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

The ester (20 g.) was allowed to react with methylmagnesium iodide (magnesium, 4·5 g.; methyl iodide, 27 g.; dry ether, 50 ml.) in the usual way, giving 6-p-*methoxyphenyl*-2-*methylhexan*-2-*ol* (VII) (15 g.), b. p. 150—151°/9 mm. (Found: C, 75·4; H, 9·8. $C_{14}H_{22}O_2$ requires C, 75·7; H, 9·9%), which (5 g.) on treatment with phosphoric acid (10 ml.) followed by distillation over sodium gave the tetralin (V) (3 g.), b. p. 127—128°/3 mm. (Found: C, 82·5; H, 9·7%).

2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-*Octahydro*-2-*oxo*-8-iso*propylnaphthalene* (IX).—Lithium (1·2 g.) was rapidly added to a stirred solution of the tetralin (V) (5 g.) in ether (25 ml.) and liquid ammonia (70 ml.) at −80°. After 20 min. ethanol (20 ml.) was introduced slowly and stirring continued until the mixture became colourless.[3] The excess of ammonia was then allowed to evaporate, the residue dissolved in water, and the liquid repeatedly extracted with ether. The ethereal solutions were washed with a solution of sodium chloride, dried (Na_2SO_4), and distilled. 1 : 2 : 3 : 4 : 5 : 8-*Hexahydro*-7-*methoxy*-1-iso*propylnaphthalene* (VIII) (4·2 g.) had b. p. 132—138°/11 mm. This was heated in ethanol (56 ml.) at 80—90° for 0·5 hr. with 2N-hydrochloric acid (50 ml.), giving the iso*propyloctalone* (IX) (2·8 g.), b. p. 150°/12 mm. (Found: C, 81·2; H, 10·4. $C_{13}H_{20}O$ requires C, 81·3; H, 10·5%), $\lambda_{max.}$ 240 mμ (ε 12,040 in EtOH). The *semicarbazone* separated from methanol as prisms, m. p. 192—193° (Found: C, 67·7; H, 9·4. $C_{14}H_{23}ON_3$ requires C, 67·5; H, 9·2%), $\lambda_{max.}$ 268 mμ (ε 23,300 in EtOH).

Condensation of 2-*Hydroxymethylene*-6-iso*propyl*cyclo*hexanone* (X) *with* 4-*Diethylaminobutan*-2-*one Methiodide*.—2-*Hydroxymethylene*-6-iso*propyl*cyclo*hexanone* (X). A mixture of 2-*iso*propyl*cyclo*hexanone [14] (b. p. 73·5°/12 mm.; 22·5 g.) and purified ethyl formate (25 g.) was added slowly with shaking to a suspension of finely divided sodium [15] (3·8 g.) in benzene (75 ml.), cooled in ice. After 12 hr. the solid sodio-salt was worked up in the usual way, giving the *hydroxymethylene ketone* (X) (20·1 g.), b. p. 106°/12 mm. (Found: C, 71·1; H, 9·5. $C_{10}H_{14}O_2$

[9] Ramart-Lucus and Amagat, *Compt. rend.*, 1929, **188**, 640.
[10] Auwers, *Annalen*, 1917, **413**, 268; Vorlander, *ibid.*, 1897, **294**, 295.
[11] Cf. Berliner, "Organic Reactions," John Wiley, New York, 1949, Vol. V, p. 263.
[12] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[13] Papa, Schwenk, and Hankin, *J. Amer. Chem. Soc.*, 1947, **69**, 3021; Pratt, Hoppe, and Archer, *J. Org. Chem.*, 1948, **13**, 578.
[14] Kotz and Michels, *Annalen*, 1906, **356**, 204.
[15] Cf. Bardhan, *J.*, 1936, 1851.

requires C, 71·4; H, 9·5%). It had a characteristic smell and gave an intense violet colour with ethanolic ferric chloride.

The compound (X) (8·4 g.) was added to a solution from sodium (1·15 g.) in absolute ethanol (20 ml.), and to the solid sodio-salt, cooled in ice, 4-diethylaminobutan-2-one methiodide (from 7·2 g. of ketone and 4 ml. of methyl iodide) in a little absolute ethanol was added all at once.[5] After 2 days at the room temperature the product was warmed at 40° for 1 hr., cooled, and mixed with a solution of potassium hydroxide (8 g.) in water (500 ml.). The clear solution gradually deposited an oil, and after 12 hr. was saturated with salt and extracted with ether. The product (3 g.) had b. p. 148—149°/10 mm. and was identical with the unsaturated ketone (IX) described above (Found: C, 80·9; H, 10·4%). The semicarbazone had m. p. 191—192° and mixed m. p. 192—193° (from methanol) (Found: C, 67·6; H, 9·3%), $\lambda_{max.}$ 268 mμ (ε 21,730 in EtOH).

1 : 2 : 3 : 4-*Tetrahydro-6-methoxy-1-oxo-4-isopropylnaphthalene* (I).—Chromic acid (19 g.) in water (9·5 g.) and acetic acid (55 ml.) was added during 2 hr. to 7-methoxy-1-*iso*propyltetralin (V) (20 g.) in acetic acid (120 ml.) at 5—10°. The liquid was stirred in the cold for 5 hr. more and then allowed to attain room temperature overnight.[6] Methanol (10 ml.) was added, the excess of acetic acid distilled off at the water-pump, the residue diluted with water, a little hydrochloric acid was added, and the whole extracted with ether in a continuous-extraction apparatus for 24 hr. After the usual washing and drying, the ethereal extract was distilled, giving the *tetralone* (I) as a pale yellow oil (16·5 g.), b. p. 181—185°/10 mm., 116°/0·05 mm. (Found: C, 76·5; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). It readily yielded a *semicarbazone* as prisms, m. p. 185—186° (from ethanol) (Found: C, 65·4; H, 7·6. $C_{15}H_{21}O_2N_3$ requires C, 65·4; H, 7·6%), a 2 : 4-*dinitrophenylhydrazone* (from acetic acid), brick red plates, m. p. 187° (Found: C, 60·2; H, 5·5. $C_{20}H_{22}O_5N_4$ requires C, 60·3; H, 5·5%), and a *piperonylidene derivative* (prepared in ethanolic sodium hydroxide), pale yellow prisms (from ethanol), m. p. 127—128° (Found: C, 74·9; H, 6·6. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%).

Synthesis of 1 : 2 : 3 : 4-*Tetrahydro-6-methoxy-1-oxo-4-isopropylnaphthalene* (I).—(a) 1-m-*Methoxyphenyl-2-methylpropan-1-ol*. *m*-Methoxybenzaldehyde (15 g.) in dry ether (20 ml.) was added to ethereal *iso*propylmagnesium bromide (magnesium, 3·7 g.; *iso*propyl bromide, 16 g.; ether, 40 ml.) cooled in ice. After being overnight at the room temperature it was worked up as usual. The *alcohol* (13 g.) had b. p. 135—138°/12 mm. (Found: C, 73·0; H, 8·8. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). The same compound was prepared, in almost equal yield, by the action of *m*-methoxyphenylmagnesium iodide [16] on *iso*butyraldehyde.

(b) The bromide was prepared by adding phosphorus tribromide (9 g.) in carbon tetrachloride (9 ml.) to the above alcohol (13 g.) in carbon tetrachloride (13 ml.) cooled in ice. After storage at the room temperature the mixture was warmed at 70° for 1 hr. The *bromide* distilled as a colourless liquid (13 g.), b. p. 130°/11 mm. (Found: Br, 33·3. $C_{11}H_{15}OBr$ requires Br, 32·9%).

(c) *Ethyl* 2-*ethoxycarbonyl*-3-m-*methoxyphenyl*-4-*methylpentanoate* (XI). The bromide (12 g.) was refluxed with ethyl sodiomalonate (sodium 1·2 g.; absolute ethanol 22 ml.; ethyl malonate, 13 g.) on the steam-bath for 10 hr., giving the *ester* (XI) (12 g.), b. p. 160°/4 mm. (Found: C, 67·2; H, 8·3. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·0%).

(d) 3-m-*Methoxyphenyl*-4-*methylpentanoic acid* (XII). The ester (XI) (26 g.) was hydrolysed with potassium hydroxide (15 g.) in water (15 ml.) and ethanol (40 ml.) in the usual way. The alkaline solution on acidification yielded an oil which was heated at 160—165° for 3 hr. and then distilled, giving the *acid* (XII) (12 g.), b. p. 168—170°/4 mm. (Found: C, 70·2; H, 8·1. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). The *ethyl ester* had b. p. 134—136°/5 mm. (Found: C, 71·9; H, 8·7. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%).

(e) 3-m-*Methoxyphenyl*-4-*methylpentan*-1-*ol* (XIII). The ester (XII) (32 g.) was reduced with sodium (32 g.) and absolute ethanol (200 ml.), giving the *alcohol* (XIII) (18 g.), b. p. 172—173°/16 mm. (Found: C, 75·2; H, 9·7. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6%). The *bromide*, prepared from the alcohol (15 g.) and phosphorus tribromide (13 g.) in dry carbon tetrachloride as described before, formed a colourless liquid (15 g.), b. p. 145—146°/8 mm. (Found: Br, 29·8. $C_{13}H_{19}OBr$ requires Br, 29·5%). The bromide (9 g.), sodium cyanide (5·5 g.), ethanol (36 ml.), and sodium iodide (1 g.) were refluxed on the steam-bath for 20 hr. The *nitrile* (6·5 g.) had b. p. 152—153°/6 mm. (Found: C, 77·1; H, 8·6. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·7%).

(f) 4-m-*Methoxyphenyl*-5-*methylhexanoic acid* (XIV). The foregoing nitrile (10·5 g.) was refluxed on the steam-bath with a solution of potassium hydroxide (5·6 g.) in water (5·6 ml.) and

[16] Bachmann and Thomas, *J. Amer. Chem. Soc.*, 1942, **64**, 95.

ethanol (12 ml.) for 40 hr. The *acid* (XIV), isolated in the usual way, was obtained as a colourless, thick oil (9·2 g.), b. p. 172—173°/4 mm. (Found: C, 71·1; H, 8·6. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

(g) **1 : 2 : 3 : 4-*Tetrahydro*-6-*methoxy*-1-*oxo*-4-iso*propylnaphthalene*** (I). The preceding acid (3 g.) was added to a stirred mixture of phosphoric acid (9 ml.; *d* 1·7) and phosphoric anhydride (12 g.) at 120°. The temperature was raised to 160° and held there for 30 min. The mixture was allowed to cool and mixed with ice, and the oil extracted with ether. The ethereal solution was washed with a solution of sodium carbonate, then with water, dried ($CaCl_2$), and distilled. The tetralone (I) formed a faint yellow liquid (2·5 g.), b. p. 154°/4 mm. (Found: C, 76·8; H, 8·2%), identical with the product described above. The semicarbazone had m. p. and mixed m. p. 185—186°, and the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 187°.

(h) *Clemmensen reduction.* The synthetic ketone (3·5 g.), amalgamated zinc (18 g.), water (10 ml.), and concentrated hydrochloric acid (40 ml.) were refluxed for 24 hr. During this period an additional quantity of concentrated hydrochloric acid (40 ml.) was added in small portions. The tetralin (2·2 g.), isolated in the usual way, on distillation over sodium had b. p. 144°/12 mm., $n_D^{20\cdot5}$ 1·5322 (Found: C, 82·3; H, 9·9%), and was identical with the compound described above.

3 : 4-*Dihydro*-7-*methoxy*-1-*methyl*-4-iso*propylnaphthalene*.—The tetralone (I) (9 g.) in dry ether (20 ml.) was added to methylmagnesium iodide (magnesium, 2 g.; methyl iodide, 6 ml.; and dry ether, 30 ml.) at 0°. The mixture was kept overnight and then refluxed for 1 hr. The crude product (8 g.) which contained an appreciable amount of unsaturated material was heated with freshly fused, powdered potassium hydrogen sulphate (16 g.) at 150° for 1 hr. The product was worked up in the usual way and distilled over sodium, giving the pure *ether* (6·5 g.), b. p. 130—134°/4 mm., 155—158°/11 mm. (Found: C, 83·2; H, 9·3. $C_{15}H_{20}O$ requires C, 83·3; H, 9·2%).

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-1-*methyl*-4-iso*propylnaphthalene*.—A solution of the foregoing ether (6 g.) in ethanol (12 ml.) was mixed with palladous chloride (0·1 g.), gum arabic (0·1 g.), and water (2 ml.) and shaken in hydrogen until a little more than 1 mol. of hydrogen was absorbed. The substituted *tetralin* formed a colourless oil (5·1 g.), b. p. 151°/10 mm. (Found: C, 82·4; H, 10·3. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%). The above ether (4·5 g.) was reduced in ether (15 ml.) with lithium (1·1 g.) and ethanol (20 ml.) in liquid ammonia (60 ml.), as described in an analogous case, giving the corresponding *derivative* (4 g.), b. p. 140—150°/10 mm. A middle fraction was analysed (Found: C, 81·8; H, 10·9. $C_{15}H_{24}O$ requires C, 81·8; H, 11·0%). This does not, however, give a solid bisulphite compound as was to be expected.[25] Further work will be necessary to clear up this point.

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888. *Border-line Mechanisms in Nucleophilic Displacement Reactions.*

By V. Gold.

The description of nucleophilic substitution reactions in the "border-line" region between pure S_N1 and S_N2 mechanisms is discussed. Some of the experimental evidence which has been held to require the postulation of intermediate mechanisms is shown to be compatible with the alternative view that such reactions are made up of concurrent unimolecular and bimolecular processes. Certain theoretical difficulties of the concept of intermediate mechanisms are pointed out.

It is now generally accepted that two distinct mechanisms of nucleophilic substitution (unimolecular or S_N1, and bimolecular or S_N2) may be recognised. The kinetics and other characteristics of these mechanisms have been extensively studied and discussed by Hughes and Ingold, and conditions for the operation of each of the mechanisms to the

exclusion of the other have been realised. There is less agreement about the description of reactions which occur under intermediate conditions, *i.e.*, at the border-line between the extreme S_N1 and S_N2 mechanisms. Such reactions are either considered to be made up of concurrent bimolecular and unimolecular processes or to possess intermediate mechanisms.[1-4]

The most direct evidence which is admissible in a discussion of the molecularity of a reaction is a kinetic examination of reaction orders. However, most of the investigated border-line reactions are solvolyses for which the establishment of reaction orders with respect to the solvent is not a straightforward matter and, consequently, unequivocal measurements of an accuracy sufficient to settle the problem do not appear to exist. We have previously shown,[5] in the case of reactions of benzoyl chloride in aqueous acetone, that an analysis of the reaction velocities in terms of concurrent unimolecular and bimolecular processes is adequate—without thereby proving that a different analysis was impossible—and have briefly indicated that the notion of intermediate molecularities could not easily be reconciled with the currently accepted theory of reaction kinetics.

The support of the view that a border-line reaction must be expressible as a sum of unimolecular (S_N1) and bimolecular (S_N2) processes (or, more generally, molecular processes of integral molecularity) has recently been described [4] as " completely indefensible." This extreme opinion is, in part, due to a use of the terms S_N1 and S_N2 in a sense which is at variance with definitions and established practice and ignores the significance [6] of the numerals 1 and 2 in the designation of the mechanisms.

The objects of the present paper are (i) to examine some of the evidence which has been thought to require the concept of reactions of intermediate molecularity, and (ii) to point out some of the general implications of the idea of intermediate molecularity.

Evidence for Intermediate Mechanisms.—(a) *Systematic study of solvent effect.* Winstein, Grunwald, and Jones [1] suggested that it was possible to arrange solvents on scales of reactivity for extreme S_N2 and S_N1 solvolyses and to give a quantitative index to the reactivity of each solvent for each of the two mechanisms. They then showed that the rate of a reaction expected to be a border-line case did not accord with the rate predicted from these solvent reactivities if the reaction were the sum of concurrent S_N1 and S_N2 processes. Their detailed procedure has been criticised by Bird, Hughes, and Ingold.[3] However, even if we accept that procedure and the results, it is not necessary to assume that the border-line reaction is anything but the sum of unimolecular and bimolecular processes.

It is common ground that in a reaction of the type

$$Y^- + R\text{–}X \longrightarrow \overbrace{Y \cdots R \cdots X}^{\text{Transition state}} \longrightarrow Y\text{–}R + X^- \qquad . \; . \; . \quad (1)$$

(y = distance between Y and R)

the role played by the nucleophilic substituting reagent Y^- diminishes in importance as we go from conditions typical for an exclusive S_N1 process towards the border-line conditions. In this progression the heterolysis of the severed bond (R–X) gradually assumes greater importance, and the formation of the new bond (R–Y) less importance, in contributing to the free-energy change on forming the transition state of the reaction from the reactants. We could also say that the distance (y) between Y and R in the transition state increases, or that Y becomes less firmly attached to R in the transition state, as we pass from the extreme S_N2 conditions to the border-line conditions. It is important to note that any transition state in which there is interaction between Y and R is a bimolecular transition state and, notwithstanding the weakness of the Y · · · R bond in the

[1] Winstein, Grunwald, and Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700.
[2] Swain and Langsdorf, *ibid.*, p. 2813.
[3] Bird, Hughes, and Ingold, *J.*, 1954, 634.
[4] Kornblum, Smiley, Blackwood, and Iffland, *J. Amer. Chem. Soc.*, 1955, **77**, 6269.
[5] Gold, Hilton, and Jefferson, *J.*, 1954, 2756.
[6] Ingold, " Structure and Mechanism in Organic Chemistry," Bell & Sons Ltd., London, 1953, pp. 310—315.

transition state, the reaction described is bimolecular (S_N2) over the whole range of this progression.

Since, in the border-line region, the interaction between Y and R is of secondary importance in the energetics of the formation of the transition state, it seems plausible to attribute comparable importance to several reaction paths which differ in the distance y of the transition state. The contribution (dv_y) to the specific rate from paths involving bimolecular transition states characterised by the length interval y to $y + dy$ would then be

$$dv_y/[RX] = k_y[Y]F_y \,.\, dy$$

where F_y is a distribution function describing the concentration of Y as a function of the distance y, *i.e.*, a measure of the ***a priori*** probability of the transition state, k_y is the appropriate rate coefficient, and [Y] the bulk concentration of Y^-. Hence the total specific rate $v/[RX]$ is given by

$$v/[RX] = [Y] \int_{y=a}^{\infty} k_y F_y \,.\, dy \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

the integration beginning at the distance of closest approach. It is impossible to specify in detail the course of the function k_yF_y. For the extreme S_N2 mechanism small values of y are expected to make the only important contribution to the integral, whereas in the border-line region k_yF_y may be significant up to larger values of y. The course of k_yF_y will therefore be expected to depend both on the nature of RX and on that of Y. In any case, the factor [Y] outside the integral indicates that the reaction is kinetically of the second order and bimolecular.

In setting up a scale of nucleophilic reactivities of different solvents for typical S_N2 reactions Winstein, Grunwald, and Jones [1] effectively chose as typical S_N2 rate constants the values of $\int k_yF_y \,.\, dy$ which apply when only small values of y need be considered. In using this scale for calculating the rates of border-line reactions—for which larger values of y still make significant contributions to the integral—they accordingly underestimate the bimolecular rate of the border-line reaction and hence observe the discrepancy on which their argument is based. Although this discrepancy indicates a gradual change in the character of the S_N2 reaction, it is no evidence—as has been claimed—against the view that there is a strictly bimolecular contribution to the total rate.

In addition to the gradual change in the bimolecular reaction on moving from the conditions for extreme S_N2 character to the border-line region, there is a gradual increase in the contribution from the reaction which does not involve Y in the transition state at all,[5] *i.e.*, the S_N1 mechanism. Hence the reaction may be described as a sum of bimolecular and unimolecular processes.

The view outlined takes into account all the phenomena on which the thesis of Winstein, Grunwald, and Jones [1] is founded. At the same time it retains the idea that there is an abrupt difference between S_N1 and S_N2 mechanisms as far as the molecularity is concerned. Such an abrupt change is a consequence of the quantisation of matter, inasmuch as there is no gradual transition between *no* molecule and *one* molecule, and it must arise in any development of reaction kinetics based on either collision or transition-state theory.

(b) *Effect of structural changes in* RX. Because of the gradual change of importance of the bond-breaking and bond-forming aspects of S_N2 reactions, the effect of a structural change in RX will in this case be less clear-cut than for S_N1 reactions where, in all cases, bond-breaking is the only phase which needs consideration. A certain substituent group may under certain conditions accelerate and under other conditions retard bimolecular reactions, since the electronic requirements of the bond-breaking and bond-forming processes are opposed. An S_N2 reaction in the border-line region for which bond-breaking is more important energetically than bond-forming will therefore show substituent effects similar to those of S_N1 reactions. Again, on going from the typical S_N2 conditions towards the border-line range and on to S_N1 conditions, we shall accordingly expect to find a gradual change in the effect of substituent groups, as was indeed observed by Swain and

Langsdorf.[2] However, these observations do not require the concept of intermediate molecularity.

Another example of structural effects in an S_N2-like reaction which follow the same order as for S_N1 reactions was recently studied in detail by Kornblum and his co-workers,[4] who found that certain heterogeneous reactions between silver nitrite and alkyl halides were accompanied by a Walden inversion but that structural changes in the alkyl halide affected the rate in the same direction as for S_N1 reactions of these halides. The evidence appears to be compatible with the hypothesis that these reactions are examples of what Ingold has termed [7] a " metal-catalysed S_N2-like substitution." Again, the conclusion that the observations required a mechanism of intermediate molecularity is not necessary.

The above views on the effect of substituents on S_N2 reactions are not novel. In particular, Baker [8] has discussed the effect of *para*-substitution in benzyl bromides [9] in the region of border-line kinetics on similar lines. The idea that the directions of substituent effects for S_N1 and S_N2 reactions must be opposite [4] in all cases is an incorrect generalisation which appears to have grown out of the studies on the effect of alkyl substituents on solvolytic reactions of methyl and ethyl halides where this difference has indeed always been observed.

General Implications of the Concept of Intermediate Molecularity.—Bird, Hughes, and Ingold [3] have reported experimental evidence of a different kind in support of the idea that mechanisms merge into each other. Their observations are those of reaction orders and, if the reactions have the general mechanism considered, are strictly relevant to the problem. It is not proposed to discuss the mechanism of these reactions or the details of the particular simplified model chosen as a basis for the physical interpretation of the results. However, the general implications of the *type* of theory proposed by Bird, Hughes, and Ingold are so wide that a brief discussion of some of its consequences seems warranted.

Their proposed rate expression for a border-line reaction (1) is equivalent to

$$-\mathrm{d[RX]}/\mathrm{d}t = \left\{k + K(1 - \mathrm{e}^{-\beta[\mathrm{Y}]})\right\}[\mathrm{RX}] \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where k, K, and β are constants of the reaction. When $\beta[Y]$ is small the expression becomes

$$-\mathrm{d[RX]}/\mathrm{d}t = \left\{k + K\beta[\mathrm{Y}]\right\}[\mathrm{RX}] \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and is of the form corresponding to concurrent first- and second-order reactions with rate constants k and $K\beta$ respectively. For large values of $\beta[Y]$, eqn. (3) can be simplified to

$$-\mathrm{d[RX]}/\mathrm{d}t = (k + K)[\mathrm{RX}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

i.e., the reaction is of first order with a rate constant $(k + K)$. For intermediate values of $\beta[Y]$ the kinetics do not follow a simple order.

If we accept the general form, eqn. 3, of the rate law then, because of the interrelation of kinetic equations and equilibrium expressions, we must be prepared to make a similar modification of the laws of chemical equilibrium. This would involve the development of more general systems of chemical and statistical thermodynamics in which chemical potentials and translational partition functions involve functions of the form $(1 - \mathrm{e}^{-\beta c})$ in place of the first power of the concentration. A further difficulty in setting up such theories is the requirement that β must be characteristic not only of the chemical species concerned but also of the reaction in which it is involved. (It is assumed that—for the simple S_N reactions—it is not necessary to consider that the reaction mechanism during the early stages of the reaction may fundamentally differ from that at equilibrium. The correctness of this assumption—which would be open to challenge in the case of less thoroughly investigated reactions, more especially when surface catalysis or chain reactions are involved—has been verified in a number of specific cases of exchange reactions in which different isotopes of a halogen constitute the nucleophilic reagents X^- and Y^-.) In fact, the incompatibility of the laws of thermodynamics with the formulation of fractional

[7] Ingold, *op. cit.*, p. 358.
[8] Baker, *Trans. Faraday Soc.*, 1941, **37**, 632.
[9] Baker and Nathan, *J.*, 1935, 1840.

reaction orders according to eqn. (3) seems insuperable. These difficulties cannot be overcome by refinement of the kinetic model and must occur with any formulation of rate laws in the general form

$$v = \left\{k + Kf([Y])\right\}[RX]$$

where the function f([Y]) has the properties that it tends to become proportional to [Y] as [Y] $\longrightarrow$ 0, and independent of [Y] as [Y] $\longrightarrow \infty$.

An alternative formulation of intermediate reaction orders would be by means of a simple power law

$$v = k[RX][Y]^{\alpha} \text{ where } 0 < \alpha < 1$$

This equation could be reconciled with the laws of chemical equilibrium but would not help to explain the results given by Bird, Hughes, and Ingold. The difficulty with this type of equation is that it implies the participation of a fractional number of molecules in a collision or a transition state and, as has been stated above, such a model is incompatible with the quantisation of matter.

It is therefore concluded that the formulation of border-line mechanisms as the concurrent operation of bimolecular and unimolecular processes is the only representation of such reactions which fits into the general body of physicochemical theory. This conclusion appears to re-open the problem of the chemical interpretation of the rate laws observed by Bird, Hughes, and Ingold.[3]

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889. *The Relation between Configuration and Conjugation in Diphenyl Derivatives. Part VII.* Halogenodiphenyls.*

By G. H. Beaven and D. Muriel Hall.

The introduction of even a single fluorine substituent into one of the *ortho*-positions of diphenyl results in a detectable blue shift and reduction in intensity of the conjugation band. In the series of 2 : 2′-dihalogenodiphenyls the blue shift and intensity reduction are progressively larger from fluorine to bromine; in 2 : 2′-di-iododiphenyl the spectrum does not show a conjugation band. In the same series, the absorption contributions due to unconjugated halogenobenzene chromophores appear with increasing distinctness as the conjugation band is inhibited, and progressively approach the expected intensity for an additive system of such absorbing units.

The ultraviolet absorption spectra of diphenyls containing fluorine substituents in the *meta*- and *para*-positions show them to be "perturbed" diphenyls, in which small changes in the conjugation band are accompanied by the appearance of low-intensity unresolved contributions from the phenyl chromophores. These minor spectroscopic effects are caused by non-steric, electronic interactions of the substituent groups with the diphenyl chromophore.

The small covalent and van der Waals radii of fluorine make it of interest to determine whether the introduction of fluorine into one or both of the *ortho*-positions of diphenyl causes sufficient additional steric hindrance to coplanarity of the phenyl groups, relative to hydrogen, for the resultant loss of conjugation across the $C_{(1)}$–$C_{(1')}$ bond to be detectable by alterations in the ultraviolet absorption spectrum. The marked effects of four chlorine atoms in the *ortho*-positions were demonstrated by Pickett, Walter, and France [1] at a time

* Part VI, *J.*, 1956, 2286.

[1] Pickett, Walter, and France, *J. Amer. Chem. Soc.*, 1936, **58**, 2296.

when the importance of coplanarity for the complete development of the intense conjugation band at *ca.* 250 mμ in diphenyl was only just being recognized. These authors showed that either chlorine atoms or methyl groups in these four positions were sufficient to cause the spectra of the derivatives to revert, more or less completely, to the additive contributions to be expected for two substituted phenyl chromophores. Williamson and Rodebush [2] found similar effects for 2 : 2′-dichlorodiphenyl and many other 2 : 2′-disubstituted diphenyls, which they related to loss of coplanarity due to steric interactions between the groups in the *ortho*-positions. The absorption spectrum of 2-iododiphenyl [3] shows similar alterations in the intensity and position of the conjugation band.

The effects of halogen in the *meta*- and *para*-positions of diphenyl, uncomplicated by steric effects, are exemplified by the spectra of appropriate compounds examined by Pickett, Walter, and France,[1] Williamson and Rodebush,[2] and Friedel and Orchin.[4]

The spectrum of 2 : 2′-difluorodiphenyl itself does not appear to have been discussed, at least in the present connection, although Bilbo and Wyman [5] compared benzidine with its 2 : 2′-difluoro-, 2 : 2′-dichloro-, 3 : 3′-dichloro-, and 2 : 2′ : 6 : 6′-tetrafluoro-derivatives and concluded that there was appreciable loss of conjugation in all the *ortho*-halogenated compounds, including the 2 : 2′-difluoro-derivative. The relative departures from coplanarity inferred from the spectra, notably from the positions of the band maxima, ran parallel with the relative reactivities of the same compounds to bromine water, in which a coplanar quinone imine intermediate with a $C_{(1)}$–$C_{(1')}$ bond of essentially double-bond character is thought to be concerned. However, the two *p*-amino-groups in benzidine may have some influence on the partial double-bond character of the $C_{(1)}$–$C_{(1')}$ collinear bond, and hence on the steric consequences of introducing *ortho*-substituents (cf.[6, 7, 8]).

The four 2 : 2′-dihalogenodiphenyls are of particular interest, since estimates of the angle (θ) between the planes of the benzene rings have been obtained by electron-diffraction.[9, 10] Littlejohn and Smith [11] have also computed values of θ which are most consistent with their dipole-moment measurements. These results are listed in Table 1, together with values for the C_{ar}–X bond lengths and van der Waals radii for the halogens. Estimates of θ in the crystalline state from *X*-ray diffraction studies on *ortho*-substituted diphenyls have been discussed earlier in this series.[12]

Apart from the surprisingly large value of θ found by Bastiansen for diphenyl itself, the most interesting feature of both the electron-diffraction and dipole results is that all four 2 : 2′-dihalogenodiphenyls have a "*cis*"-conformation, corresponding to halogen–halogen contacts, rather than a "*trans*"-conformation, with halogen–hydrogen contacts, that might have been expected from a simple consideration of electrostatic repulsion. (Mason and Kreevoy [13] have considered F–F and Cl–Cl interactions in a theoretical study of barriers to internal rotation about single bonds and find the Coulombic interaction to be only *ca.* 10% of the total repulsion energy, of which about half is due to ordinary van der Waals repulsions.) Although in the crystalline state the two nuclei of diphenyl itself appear to be coplanar, Pauling [14] drew attention to the possibility of steric interactions between the hydrogens in the four *ortho*-positions. Previous electron-diffraction work by Karle and Brockway [15] tends to support Bastiansen's non-coplanar conformation for the

[2] Williamson and Rodebush, *J. Amer. Chem. Soc.*, 1941, **63**, 3018.
[3] Dunn and Iredale, *J.*, 1952, 1592.
[4] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," Wiley and Sons, Inc., New York, 1951, No. 183.
[5] Bilbo and Wyman, *J. Amer. Chem. Soc.*, 1953, **75**, 5312.
[6] Pickett, Groth, Duckworth, and Cunclife, *ibid.*, 1950, **72**, 44.
[7] Sherwood and Calvin, *ibid.*, 1942, **64**, 1350.
[8] Calvin, *J. Org. Chem.*, 1939, **4**, 256.
[9] Bastiansen, *Acta Chem. Scand.*, 1949, **3**, 408; 1950, **4**, 926.
[10] Bastiansen and Smedvik, *ibid.*, 1954, **8**, 1593.
[11] Littlejohn and Smith, (*a*) *J.*, 1953, 2456; (*b*) *J.*, 1954, 2552.
[12] Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854.
[13] Mason and Kreevoy, *J. Amer. Chem. Soc.*, 1955, **77**, 5808.
[14] Pauling, "The Nature of the Chemical Bond," Cornell University Press, 1942, 2nd edn., p. 220.
[15] Karle and Brockway, *J. Amer. Chem. Soc.*, 1944, **66**, 1974.

vapour state, though Rousset and Pacault [16] concluded from light-scattering studies that in *cyclo*hexane solution the anisotropy of polarisibility of diphenyl was much greater than that of benzene, to an extent which suggested a highly conjugated and essentially planar conformation.

In considering the absolute magnitudes of θ estimated by electron diffraction, it must be remembered that these are equilibrium values. Torsional vibrations about the

TABLE 1. *2 : 2′-Dihalogenodiphenyls and related compounds.*

Halogen	C_{ar}–Hal bond length (Å) [a]	van der Waals radius of halogen (Å) [b]	Angle between planes of benzene rings, θ: Electron diffraction [c]	Dipole moment [d]	Calc. [e] "*cis*"	Calc. [e] "*trans*"
(H)	(1·04)	(1·20) [b]	45 ± 10°	—	42° [b]	
F	1·35	1·35	60 ± 5° (*cis*) [d]	77° [f]	55°	49°
Cl	1·69	1·80	74 ± 5° (*cis*)	81° [f]	79°	64°
Br	1·88	1·95	75 ± 5° (*cis*)	85°	83°	67°
I	2·00	2·15	79 ± 5° (*cis*)	84°	91°	72°
2-Fluoro	1·35	1·35	49 ± 5° [d]	—	49°	
4 : 4′-Difluoro	—	—	44 ± 5° [d]	—	(42°)	

[a] Electron diffraction; Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46. [b] Pauling, ref. 14, p. 189. [c] Bastiansen.[9] [d] Bastiansen and Smedvik.[10] [e] Littlejohn and Smith.[11b] [f] Revised values based on bond lengths given in the second column; J. W. Smith, personal communication. [g] Values calculated by using data from *a* and *b* and $C_{(1)}$–$C_{(1')}$ 1·50 Å, C–C_{ar} 1·40 Å. [h] For a van der Waals radius of 1·0 Å for hydrogen, θ for diphenyl is reduced to 23°.

$C_{(1)}$–$C_{(1')}$ bond were indicated by the data, but the amplitudes of these vibrations were not evaluated, though procedures are becoming available.[17]

Bastiansen calculated that the halogen–halogen distances corresponding to the observed values of θ were slightly less than twice the appropriate van der Waals radii for all the 2 : 2′-dihalogenodiphenyls except the difluoro-compound. The last column in Table 1 shows the values of θ calculated for conformations in which the *ortho* atoms are "touching," *i.e.*, the distance between the atomic nuclei is the sum of the van der Waals radii. Strictly, van der Waals radii apply to intermolecular contacts and not to approaches between atoms in the same molecule; however, a 2 : 2′-dihalogenodiphenyl could presumably take up (without strain) a conformation in which the halogen distance is *greater* than twice the van der Waals radius so that it seems justifiable to regard the contact between the two halogen atoms as of the intermolecular rather than of the intramolecular type. Other "interference radii" have been used by some workers but the choice is to a certain extent dependent on the physical property and the type of molecule under consideration (cf. Kofod, Kumar, and Sutton; [18] Braude and Sondheimer [19]); in the absence of unequivocal data on which to base adjustments to the covalent bond radii it seems preferable to use van der Waals radii to study steric interference in the 2 : 2′-dihalogenodiphenyls.

Calculations of θ for compounds of this type have a rather different significance from those for *ortho*-bridged diphenyls. In the latter the configuration of the diphenyl skeleton is fixed within fairly narrow limits by the bridging ring, and considerable distortion is required to change θ by more than a few degrees. Also the data required for the calculations are normal covalent radii, not van der Waals radii, and are thus subject to less ambiguity. In the non-bridged compounds, however, the "touching" conformation (for which θ has been calculated here) is only one of many possible conformations; even if it should, in fact, correspond to a preferred conformation there will be other conformations (with different values of θ) of only slightly higher energy.

[16] Rousset and Pacault, *Compt. rend.*, 1954, **238**, 1705.
[17] Karle, *J. Chem. Phys.*, 1954, **22**, 1246, and earlier papers; Bartell, Brockway, and Schwendeman, *ibid.*, 1955, **23**, 1854.
[18] Kofod, Kumar, and Sutton, *J.*, 1951, 1790.
[19] Braude and Sondheimer, *J.*, 1955, 3754.

The overlaps between the *ortho*-atoms for the 2 : 2′-dihalogenodiphenyls are conventionally depicted in Fig. 1, van der Waals radii and a $C_{(1)}$–$C_{(1')}$ bond length of 1·50 Å (Bastiansen,[9] electron diffraction; corresponding to *ca.* 10% double-bond character) being used, and showing both "*cis*" (halogen-halogen) and "*trans*" (halogen–hydrogen) overlaps.

FIG. 1. *Plane projection scale diagram of* 2 : 2′*-substituent overlaps in diphenyl, van der Waals radii being used.*
Top: Halogen–halogen ("*cis*") overlaps.
Bottom: Hydrogen–halogen ("*trans*") overlaps.

Excellent spectra of the monohalogenobenzenes are available,[20] though in *iso*octane solution, and not extending below 220 mμ. Results for ethanolic solution,[21] which do not include iodobenzene, show the expected small differences in wavelengths and intensity. The available data for the *o*-halogenotoluenes [22] are older and also refer to hydrocarbon solvents. The results show, however, small long-wave shifts and intensity changes due to

TABLE 2. *Ultraviolet absorption spectra of fluorodiphenyls.*

	Conjugation band				Long-wave band			
Diphenyl	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{max.}$	$\varepsilon_{max.}$
Diphenyl	222	4300	249	17,300	—	—	—	—
2-Fluoro-	219·5	5500	241·5	16,500	—	—	(281)	(1600)
							(274)	(3000)
2 : 2′-Difluoro-	216	7100	233·5	13,800	259	3000	268	3400
2-Fluoro-4 : 4′-dimethyl-	223·5	6000	248·5	20,000	—	—	(278·5)	(5000)
							(276)	(5500)
2 : 2′-Difluoro-4 : 4′-dimethyl-	221	8700	240	18,500	266·5	4900	271	5150
3 : 3′-Difluoro-	222	4800	247	15,500	—	—	(279·5)	(5000)
							(275·5)	(5700)
4-Fluoro-	221·5	4300	247·5	16,900	—	—	(273)	(4000)
							(262·5)	(8800)
4 : 4′-Difluoro-	220	3600	245	15,000	—	—	(271·5)	(4000)
							(263·5)	(7000)
4 : 4′-Difluoro-3 : 3′-dimethyl-	225·5	4700	247	14,000	—	—	(277·5)	(2900)
							(265·5)	(6000)

Wavelengths in mμ; figures in parentheses refer to inflections; solvent 96% ethanol.

the available data for the *o*-halogenotoluenes [22] are older and also refer to hydrocarbon solvents. The results show, however, small long-wave shifts and intensity changes due to

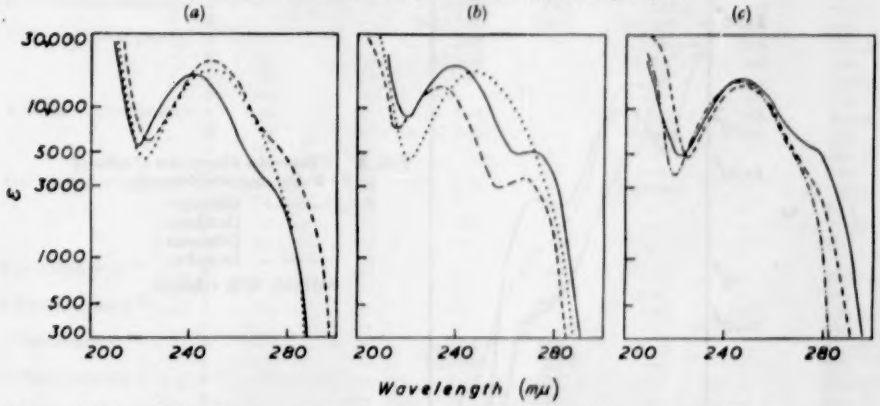
[20] American Petroleum Institute, Research Project No. 44, Ultraviolet Spectral Data, Serial nos. 296, 300, 304, 308.
[21] Robertson and Matsen, *J. Amer. Chem. Soc.*, 1950, **72**, 5252.
[22] Conrad-Billroth, *Z. phys. Chem.*, 1934, *B*, **25**, 139; Wolf and Herold, *ibid.*, 1931, *B*, **13**, 201.

the introduction of the alkyl group. The intensity change is small for *o*-fluorotoluene, but increases through the series to *ca.* 100% for the bromo- and chloro-derivatives. Taken as a whole the literature data are adequate for comparison with the spectra of the 2 : 2'-dihalogenodiphenyls.

It is convenient to consider the results for the fluorodiphenyls (Table 2), including the 2 : 2'-difluoro-derivative, before discussing the 2 : 2'-dihalogenodiphenyls as a separate group.

The spectrum of 2-fluorodiphenyl (Fig. 2*a*), compared with that of diphenyl, shows a small short-wave (blue) shift and slight reduction in intensity of the conjugation band, and also a distinct long-wave double inflection. In 2-fluoro-4 : 4'-dimethyldiphenyl the introduction of the methyl groups results in the conjugation band having nearly the same intensity as in 4 : 4'-dimethyldiphenyl ($\lambda_{max.}$ 253 mμ, $\epsilon_{max.}$ 21,100),[23] but at shorter wavelength. The higher intensities of the long-wave inflections in 2-fluoro-4 : 4'-dimethyldiphenyl are obviously due to increased overlapping by the conjugation band. A further

FIG. 2. *Ultraviolet absorption spectra of fluorodiphenyls.*



(*a*) —— 2-Fluorodiphenyl. — — — 2-Fluoro-4 : 4'-dimethyldiphenyl. . . . . Diphenyl.
(*b*) —— 2 : 2'-Difluorodiphenyl. — — — 2 : 2'-Difluoro-4 : 4'-dimethyldiphenyl. . . . . Diphenyl.
(*c*) —— 3 : 3'-Difluorodiphenyl. – – – – 4 : 4'-Difluoro-3 : 3'-dimethyldiphenyl. —·—·— 4 : 4'-Difluorodiphenyl. Solvent, 96% ethanol.

indication of the effect of the *p*-methyl groups is the shift of the minimum on the short-wave side of the conjugation band.

In 2 : 2'-difluorodiphenyl (Fig. 2*b*), the short-wave shift and reduction in intensity of the conjugation band are very marked, and the long-wave feature is a shallow but distinctly resolved maximum. The effects of introducing methyl groups into the two *para*-positions are qualitatively similar to those for 2-fluorodiphenyl, but the apparent compensation for the steric effect of two *o*-fluoro-substituents on the position and intensity of the conjugation band is less than in the 2-fluoro-compound.

It may be concluded that the steric effect of even one *o*-fluoro-substituent in diphenyl is sufficient to affect the conjugation band to an easily detectable extent.

The other four compounds listed in Table 2, containing fluorine in non-*ortho*-positions, all show small reductions in intensity and slight blue shifts of the conjugation band, compared with diphenyl (Fig. 2*c*), and all have faint long-wave inflections, which are most easily detectable by the moving-plate, logarithmic-cam photographic method. The observed intensities of these inflections are obviously determined very largely by the overlapping conjugation bands in all four compounds.

[23] O'Shaughnessy and Rodebush, *J. Amer. Chem. Soc.*, 1940, **62**, 2906; ref. 2.

The small short-wave shifts of the conjugation band suggest that the inductive and mesomeric effects of the fluorine substituents are giving rise to opposing blue and red shifts of nearly equal magnitude, as suggested by Cooper [24] (cf. Smith and Turton [25]) for fluorobenzene. The cancellation of blue-shifts and summation of red-shifts proposed by this author to explain the large red-shift in *p*-difluorobenzene does not seem to apply to the diphenyls with 4 : 4′-difluoro-substituents. The effects of these substituents are in striking contrast to those of chlorine, bromine, and iodine in the same positions, which give rise to progressively larger red shifts and intensity increases of the conjugation band [2, 4] analogous to the effects in the corresponding 1 : 4-dihalogenobenzenes. Friedel and Orchin's curve for 4 : 4′-dichlorodiphenyl shows some very faint long-wave fine structure in the 280—300 mμ region, with extinction coefficients in the 100—1000 range, which may be analogous to the fine structure in 4 : 4′-difluorodiphenyl. Apart from this, the 4 : 4′-difluoro-substituents are clearly exceptional, compared with the other halogens, in not producing an increase in intensity of the conjugation band, as well as in causing a small blue shift.

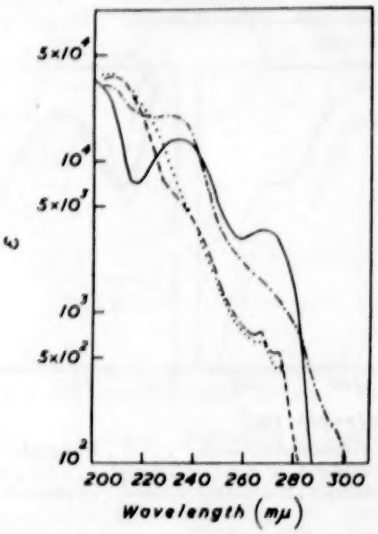


FIG. 3. *Ultraviolet absorption spectra of 2 : 2′-Dihalogenodiphenyls.*

——— Difluoro-.
— — — Dichloro-.
. . . . . Dibromo-.
—·—·— Di-iodo-.

Solvent, 96% ethanol.

It is of interest to note that in 4 : 4′-difluoro-3 : 3′-dimethyldiphenyl, although the spectrum shows the expected red shift due to the introduction of the methyl groups, the conjugation band is still further reduced in intensity, consistent with the effect of 3 : 3′-dimethyl substituents alone.[23] The overall effect on the diphenyl conjugation band of introducing a single fluorine into the 4-position is very slight, apart from the appearance of the long-wave inflections.

On the basis of the long-wave absorption features, these non-*ortho*-substituted diphenyls can all be regarded as " perturbed " diphenyls, in the sense that the term is used by Wentzel.[26] The effects of these substituent groups, including the reduced intensity of the conjugation band, can alternatively be accounted for on the basis of their electronic interaction with the benzene rings in such a manner as to reduce slightly the conjugation across the $C_{(1)}$–$C_{(1')}$ bond (cf. Part I [12]). The two viewpoints are essentially identical, except that Wentzel, following Platt,[27] considers that the benzene-type transition, which gives rise to

[24] Cooper, *J. Chem. Phys.*, 1954, **22**, 503.
[25] Smith and Turton, *J.*, 1951, 1701.
[26] Wentzel, *J. Chem. Phys.*, 1953, **21**, 403.
[27] Platt, *ibid.*, 1951, **19**, 101.

the long-wave inflections in " perturbed " diphenyls, must also be present, for theoretical reasons, in diphenyl itself but is obscured by the conjugation band.

For the fluorine-substituted diphenyls, the intensity changes alone do not differentiate the *ortho*-substituted from the other derivatives. The magnitudes of the wavelength shifts are clearly of greater importance but even here allowance must be made for the (bathochromic) effects of the methyl groups.

The spectra of the other 2 : 2′-dihalogenodiphenyls (Fig. 3 and Table 3) differ markedly from that of the 2 : 2′-difluoro-derivative. In the dichloro-derivative the conjugation band has suffered a further blue shift and reduction in intensity and takes the form of a broad inflection at *ca.* 230 mμ of about one-third the extinction coefficient of diphenyl

TABLE 3. *Ultraviolet absorption spectra of 2 : 2′-dihalogenodiphenyls, halogenobenzenes, and o-halogenotoluenes.*

		Short-wave bands.				Conjugation band		Long-wave band
Compound			min.	max.	min.	max.	min.	max.
2 : 2′-Difluorodiphenyl	λ	—	—	<200	216	233·5	259	268
	ε	—	—	>35,000	7100	13,800	3000	3400
2 : 2′-Dichlorodiphenyl	λ	—	—	208	—	(230)	264	273·5
	ε	—	—	36,000	—	6,600	700	540
	λ	—	—	—	—	—	—	266·5
	ε	—	—	—	—	—	—	735
2 : 2′-Dibromodiphenyl	λ	—	—	*ca.* 206	—	(*ca.* 228) *	265	274·5
	ε	—	—	*ca.* 37,000	—	12,000	620	430
	λ	—	—	—	—	—	—	267·5
	ε	—	—	—	—	—	—	640
2 : 2′-Di-iododiphenyl	λ	*ca.* 204	222	230	—	Absent	—	(*ca.* 280)
	ε	*ca.* 32,000	19,700	—	—	—	—	840
	λ	—	—	19,100	—	—	—	(*ca.* 273)
	ε	—	—	—	—	—	—	1200
Fluorobenzene [20]	λ	—	—	—	222	—	—	260 fs
	ε	—	—	—	6·7	—	—	1060
o-Fluorotoluene [22]	λ	—	—	—	—	—	—	268 fs
	ε	—	—	—	—	—	—	910
Chlorobenzene [20]	λ	—	—	<219	235	—	—	265 fs
	ε	—	—	>5700	22·3	—	—	236
o-Chlorotoluene [22]	λ	—	—	—	237	—	—	266 fs
	ε	—	—	—	37	—	—	390
Bromobenzene [20]	λ	—	—	(223)	248	—	—	265 fs
	ε	—	—	5940	161	—	—	204
o-Bromotoluene [22]	λ	—	—	—	250	—	—	267 fs
	ε	—	—	—	130	—	—	420
Iodobenzene [20]	λ	—	*ca.* 215	228 fs	244	—	—	258 fs
	ε	—	*ca.* 6900	13,300	534	—	—	693
o-Iodotoluene [22]	λ	—	—	—	252	—	—	261 fs
	ε	—	—	—	900	—	—	1130

* Very faint.

Wavelengths in mμ; figures in parentheses refer to inflections; fs denotes resolved fine structure, with figures given for principal maxima. Solvents: diphenyls, 96% ethanol; halogenobenzenes,[20] *iso*octane; *o*-halogenotoluenes,[22] hexane.

itself, and even this is to some extent due to overlapping by more intense bands at much shorter wavelength. In 2 : 2′-dibromodiphenyl there is a very faint inflection at *ca.* 228 mμ; the total intensity in this region is about twice that of the dichloro-derivative, presumably because of a larger red shift of the intense short-wave bands. In 2 : 2′-di-iododiphenyl the spectrum is quite different, showing a broad but resolved band with a maximum at 230 mμ, well separated from the band at shorter wavelength, which is of rather lower intensity than in the other 2 : 2′-dihalogenodiphenyls. Comparison of this spectrum with those of iodobenzene and iodotoluene strongly suggested that the 230 mμ band can be identified as that of the iodophenyl chromophore, occurring at about the same wavelength but showing some vibrational fine structure in iodobenzene; its intensity (*ca.* 20,000) is also comparable with the expected value (*ca.* 27,000) for two

iodophenyl groups. The spectrum of 2 : 2′-di-iodiphenyl is therefore that of a severely hindered and markedly non-coplanar diphenyl, in which there is no evidence of conjugation and which is qualitatively, and to a large extent quantitatively, in agreement with the additive absorption of two independent iodophenyl chromophores.

The spectra of 2 : 2′-dichlorodiphenyl (cf. Friedel and Orchin [28]) and of 2 : 2′-dibromodiphenyl also exhibit resolved low-intensity long-wave fine structure. In the 2 : 2′-di-iodo-derivative the only long-wave features are two faint inflections. As in 2 : 2′-difluorodiphenyl, these long-wave features can be regarded as absorption contributions of the halogenobenzene partial chromophores, but with intensities determined to varying extents by overlapping conjugation band contributions.

Quantitative comparisons with the spectra of the *o*-halogenotoluenes are best made at the wavelengths corresponding to the principal long-wave maxima and the principal minima of these compounds. The ratios listed in Table 4 are the extinction coefficients of the diphenyls divided by *twice* the extinction coefficients of the corresponding *o*-halogenotoluenes, at these wavelengths. If the total absorption of the diphenyl were simply the additive contributions of two non-conjugated halogenophenyl chromophores, these ratios should be about unity. Table 4 shows that for the longer wavelength comparison ($\lambda_{max.}$ of

TABLE 4. *Comparison of molecular-extinction coefficients of 2 : 2′-dihalogenodiphenyls and corresponding o-halogenotoluenes at selected wavelengths.*

Halogen	λ_1 [a]	$\varepsilon_{DP}/2\varepsilon_T$ [b]	λ_2 [c]	$\varepsilon_{DP}/2\varepsilon_T$
(H)	262 [d]	17	231 [d]	163
F	268	1·9	235 [e]	98 [f]
Cl	266	0·93	237	63
Br	267	0·76	250	5·5
I	261	0·87	252	1·7

[a] Wavelength of principal maximum of *o*-halogenotoluene, mμ; ethanol. [b] Molecular-extinction coefficients of 2 : 2′-dihalogenodiphenyl (ε_{DP}) and of corresponding *o*-halogenotoluene (ε_T), both at the indicated wavelength. [c] Wavelength of minimum of *o*-halogenotoluene, mμ; ethanol. [d] Toluene in ethanol (data from references given by Jones, *Chem. Rev.*, 1943, **32**, 1). [e] Estimated, short extrapolation. [f] From data for fluorobenzene.

o-halogenotoluene) the ratio is approximately unity for the dichloro-, dibromo-, and di-iodo-diphenyls, but nearly 2 for 2 : 2′-difluorodiphenyl, in which the conjugation band makes an appreciable contribution to the total absorption at this wavelength. At the shorter wavelength ($\lambda_{min.}$ of *o*-halogenotoluene) the ratio is very much greater than unity for all but the iodo-derivatives, indicating that the total absorption in this region still contains a contribution from a conjugation band, even in the case of 2 : 2-dibromodiphenyl.

The 2 : 2′-dihalogenodiphenyls thus form a series in which the spectroscopic indications of conjugation and of halogenophenyl partial chromophore absorption vary continuously from the slightly hindered difluoro-compound to the severely hindered di-iodo-compound.

In spite of the uncertainty attaching to the values of θ for non-bridged diphenyls, it is of interest to compare the spectra of such compounds with those of bridged diphenyls having similar angles between the benzene ring planes. For a compound with an *ortho* : *ortho′* bridge of three carbon atoms θ is 49° and with a bridge of four carbon atoms θ is 59° (calculated values). In the latter case (*e.g.*, in dimethyl 4 : 5-6 : 7-dibenz*ocyclo*octa-4 : 6-diene-1 : 2-carboxylate [29]) the conjugation band ($\lambda_{max.}$ 236·5 mμ, $\varepsilon_{max.}$ *ca.* 13,000) shows a blue shift and a reduction in intensity comparable to that shown by 2 : 2′-difluorodiphenyl. The similarity between the value of θ for the bridged compound and that (electron diffraction or calculated) for 2 : 2′-difluorodiphenyl is striking. Equally striking is the correlation between the great reduction in conjugation, judged spectroscopically, and the large increase in θ in passing from the difluoro- to the dichloro-compound.

The 2 : 2′-dialkyldiphenyls are a simpler series of compounds in which to study the

[28] Friedel and Orchin, ref. 4, No. 182.
[29] Beaven, Bird, Hall, Johnson, Ladbury, Lesslie, and Turner, *J.*, 1955, 2708.

spectroscopic effects of *ortho*-substitution in the diphenyl structure. However, the smallest alkyl group (methyl) is of comparable size to bromine (van der Waals radii 2·0 and 1·95 Å, respectively); whereas only with fluorine as an *ortho-ortho'* substituent is the value of θ (calculated for the "*cis*" "touching" conformation) small enough to be comparable with those calculated for the 2 : 2'-bridged diphenyls. The persistence of the conjugation band in 2 : 2'-difluorodiphenyl and in the bridged compounds and its almost complete repression in the 2 : 2'-dialkyldiphenyls [30] and in the other 2 : 2'-dihalogenodiphenyls therefore appear in both series of compounds to be consistent with the calculated θ values.

An interesting spectroscopic confirmation of the steric effects of 2 : 2'-difluoro- and 2 : 2'-dichloro-substituents in diphenyl comes from the study by Lewis and Kasha [31] of the phosphorescence spectra involving a triplet excited state with a central double bond (I and related resonance structures; each asterisk denoting an unpaired electron). Compared with diphenyl (wavenumber, $\tilde{\nu}_p$, of highest frequency phosphorescence band, 22,800 cm.$^{-1}$) the halogenated derivatives show blue shifts of 1600 cm.$^{-1}$ (2 : 2'-difluoro) and 2200 cm.$^{-1}$ (2 : 2'-dichloro), due to steric inhibition of the resonance stabilization of the triplet excited state. From a comparison with the $\tilde{\nu}_p$ value for 2 : 2' : 6 : 6'-tetrachlorodiphenyl, Lewis and Kasha concluded that the inhibtion was substantially complete with

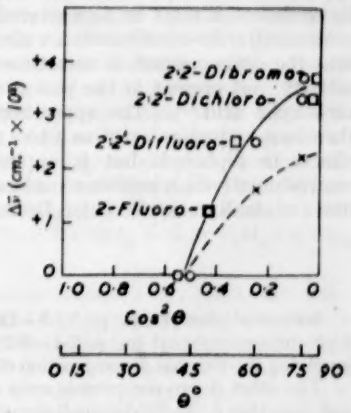
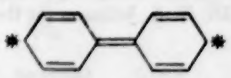


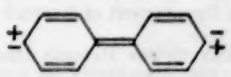
FIG. 4. *Frequency shift ($+\Delta\tilde{\nu}$) of conjugation band maximum against $\cos^2\theta$ (θ = angle between planes of benzene rings).*

○ Values of θ from electron diffraction.
□ Calculated values of θ for the "*cis*" conformation.
× Frequency shifts ($+\Delta\tilde{\nu}_p$) of triplet-singlet phosphorescence band.

two *o*-chloro-substituents. The magnitudes of the blue shifts of $\tilde{\nu}_p$ in the phosphorescence spectra are compared with the shifts ($\Delta\tilde{\nu}$) of the conjugation band of the ordinary absorption spectra (singlet-singlet transitions) in Fig. 4.



(I)



(II)

If the excited state of diphenyl is a dipolar (and more nearly coplanar) structure with a $C_{(1)}$–$C_{(1')}$ linkage of essentially complete double-bond character (*e.g.*, II; cf. Calvin,[8] Braude [32]) then the short-wave shift of the conjugation band in an *ortho*-halogenodiphenyl might arise from an increase in transition energy due mainly to a raising of the energy of the *excited* state, which will be more sensitive to *ortho*-steric effects than the ground state. On this basis a correlation might be expected between the steric requirements of the *ortho*-substituents, as indicated by the angles between the planes of the benzene rings in the

[30] Beaven, Hall, Lesslie, Turner, and Bird, *J.*, 1954, 131; Everitt, Hall, and Turner, *J.*, 1956, 2286.
[31] Lewis and Kasha, *J. Amer. Chem. Soc.*, 1944, **66**, 2100.
[32] Braude, *Experentia*, 1955, **11**, 457.

ground state, and the short-wave shift, expressed on an energy scale (*i.e.*, $\Delta\tilde{\nu}$). In fact, the electron-diffraction or calculated values of θ (Table 1) being used, plots of $\Delta\tilde{\nu}$ (from Table 3) against $\cos^2\theta$ (cf. Dewar [33]) fall on a smooth curve (Fig. 4). The $\Delta\tilde{\nu}_p$ values for the triplet states of 2 : 2′-difluoro- and 2 : 2′-dichloro-diphenyl also show a correlation with $\cos^2\theta$, though the smaller frequency shifts are at variance with the expectation that the triplet excited state is extremely sensitive to steric strain (Lewis and Kasha [31]). In view of the large effects of halogen substituents on the intensities and transition energies of aromatic chromophores the broad correlation between θ and $\Delta\tilde{\nu}$ is perhaps as good as can be expected, and other series of substituted diphenyls may provide spectroscopic data more suitable for analysis along these lines.

The smallest blue shift, not complicated by methyl-group effects, observed in the present work is 1300 cm.$^{-1}$ (3·7 Kcal./mole) for 2-fluorodiphenyl; for the 2 : 2′-difluoro-compound $\Delta\tilde{\nu}$ is 2700 cm.$^{-1}$ (7·7 Kcal./mole). For comparison, the blue shift in the triplet state of the 2 : 2′-difluoro-compound is $\Delta\tilde{\nu}_p = 1600$ cm.$^{-1}$ (4·6 Kcal./mole). For the introduction of substituents into diphenyl itself, changes of this magnitude in the energy barrier to free rotation could not give rise to optical activity detectable by any known technique; among diphenyls with *o*-halogeno-substituents unstable optical activity first appears with a dibromo-derivative, in 2 : 2′-dibromodiphenyl-4 : 4′-dicarboxylic acid.[34] Nevertheless, it must be remembered that in a more hindered diphenyl (*i.e.*, one in which some small *ortho*-substituents are already present) the introduction of a single fluorine atom into the *ortho*-position is sometimes sufficient to produce observable (unstable) optical activity, not present in the parent compound (*e.g.*, 2′-fluoro-5′-methyl-6-nitrodiphenyl-2-carboxylic acid [35]). The appearance of (unstable) optical isomerism may on occasion, therefore, be just as sensitive a tool as ultraviolet absorption for the investigation of steric effects in diphenyls but is applicable to a different range of compounds. Optical resolvability (which implies considerable optical stability) is, however, a much less sensitive index of small steric effects (cf. Braude and Waight [36]).

Experimental

2-Fluorodiphenyl (m. p. 72·5—73·5°), 2 : 2′-difluorodiphenyl (m. p. 118·5—119·5°), and 3 : 3′-difluorodiphenyl (m. p. 7·1—7·2°, b. p. 102°/2 mm.) were made by the standard method involving the thermal decomposition of a diazonium borofluoride.

The other fluoro-compounds were made available to us by Professor E. E. Turner, F.R.S., and the other 2 : 2′-dihalogenodiphenyls by Dr. J. W. Smith.

The spectra were measured on a Unicam SP. 500 spectrophotometer. Fine structure and inflections were detected photographically by the logarithmic-cam, moving-plate method.[37]

We thank Professor E. E. Turner, F.R.S., for his interest and encouragement in this work. We are indebted to him and to Dr. J. W. Smith for gifts of chemicals and to Dr. R. G. Taylor of the Mathematics Department of Bedford College and Dr. E. A. Johnson for the calculations.

National Institute for Medical Research.
Bedford College, University of London. [*Received, June 8th*, 1956.]

[33] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3345.
[34] Searle and Adams, *J. Amer. Chem. Soc.*, 1934, **56**, 2112.
[35] Stoughton and Adams, *ibid.*, 1932, **54**, 4426.
[36] Braude and Waight, "Progress in Stereochemistry," Vol. I (Ed. Klyne), Butterworths, London, 1954, p. 143.
[37] Holiday, *J. Sci. Instr.*, 1937, **14**, 166.

890. *Friedel–Crafts Acylation and Alkylation. A Comparison of Inter- and Intra-molecular Processes.*

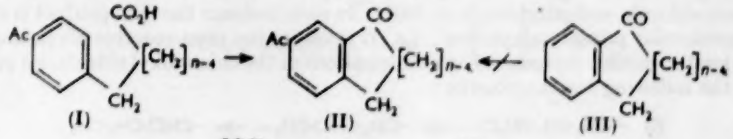
By G. Baddeley and R. Williamson.

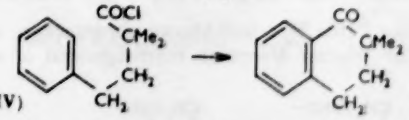
The following comparisons are illustrated and discussed: (i) Phenyl groups which are deactivated towards electrophilic substitution by carboxyl or acyl substituents and thereby made incapable of undergoing intermolecular acylation may participate in intramolecular acylation if this provides a 5- or 6-membered ring. (ii) Intramolecular alkylation which involves the formation of a 5-, 6-, or 7-membered ring is less affected by isomerisation of the alkylating agent than is intermolecular alkylation and provides ready primary alkylation of a phenyl group which has an acyl substituent. (iii) Cyclisation of halogenoalkyl phenyl ketones occurs more readily and is less affected by isomerisation than is that of *p*-chloroalkylacetophenones.

It is well known that intramolecular reactions effecting the formation of five- and six-membered rings occur more readily than the corresponding intermolecular processes. This paper illustrates the major differences between inter- and intra-molecular acylation and alkylation of phenyl groups by the Friedel–Crafts process and the effect thereon of replacing phenyl by acetylphenyl groups.

Acylation.—Intermolecular acylation of monoalkylbenzenes affords only monoacyl derivatives and attempts to enforce diacylation, *e.g.*, by raising the temperature, usually cause (*a*) decomposition of the acylating agent and (*b*) dehydrogenation of the alkyl substituent (forthcoming communication). For example, reaction of acetylating agent with 4-ethylacetophenone requires a temperature of *ca.* 100° and gives (*a*) acetylacetone and other products of decomposition of the acetylating agent, and (*b*) *p*-acetylbenzylideneacetone, the final product of the interaction of the acylating agent and the ethyl substituent: $p\text{-Ac}\cdot C_6H_4\cdot CH_2\cdot CH_3 + Me\cdot COCl,AlCl_3 \longrightarrow HCl + Me\cdot CHO,AlCl_3 + p\text{-Ac}\cdot C_6H_4\cdot CH{:}CH_2 \xrightarrow{Me\cdot COCl,AlCl_3} p\text{-Ac}\cdot C_6H_4\cdot CH{:}CHAc$.

On the other hand, intramolecular acylation of aromatic ketones is comparatively easy: *e.g.*, whereas indan-1-one and 1-tetralone (III; $n = 5$ and 6 respectively) cannot be acetylated, their acetyl derivatives (II) are readily obtained by cyclisation of β-*p*-acetylphenylpropionic (I; $n = 5$) and γ-*p*-acetylphenylbutyric acid (I; $n = 6$) through the agency of aluminium chloride.[1] Similarly, the dicarboxylic acids obtained by hypochlorite oxidation of the keto-acids (I; $n = 5$ and 6) are readily converted into 1-oxoindane-6-carboxylic acid and 1-tetralone-7-carboxylic acid respectively.[1]



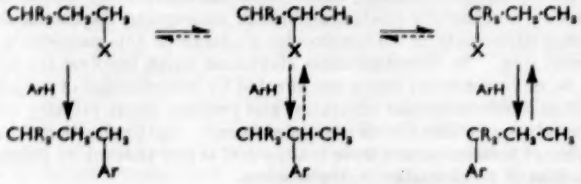


In further illustration of the comparative ease of intramolecular acylation is the fact that the decarbonylation process, $RR'R''C\cdot COCl,AlCl_3 \longrightarrow RR'R''CCl,AlCl_3 + CO$, which interrupts the Friedel–Crafts acylation of benzene and its derivatives by tertiary acid chlorides, is of no account in the cyclisation of αα-dimethyl-γ-phenylbutyryl chloride (IV). However, this process is interrupted by decarbonylation when the reactivity of the phenyl groups towards acylating agent is low: thus carbon monoxide is evolved in the reaction of αα-dimethyl-γ-*p*-acetylphenylbutyryl chloride (VII) with aluminium chloride; the other

[1] See Experimental section.

product, 7-acetyl-1 : 2 : 3 : 4-tetrahydro-2-methylnaphthalene (VI), is afforded by intramolecular primary alkylation.[1]

Alkylation.—Isomerisation of the alkylating agent is a feature of the Friedel–Crafts alkylation of benzene and its homologues, and the products of monoalkylation are determined (*a*) by the relative rates of the several reactions indicated in the scheme below and (*b*) by the extent to which the reaction mixture is allowed to approach equilibrium composition.



Some of the more important considerations are : (i) Alkyl halide readily isomerises in the direction primary ⟶ secondary ⟶ tertiary; reversal of these changes is less ready. (ii) The reactivity of alkyl cation as electrophilic reagent decreases in the order primary > secondary > tertiary. (iii) Ease of reversal of the alkylation process increases in the order primary < secondary < tertiary; in fact, primary alkylation at room temperature is irreversible. (iv) Acetophenone is much less reactive towards alkylating agent than is benzene and attempts to alkylate the former provide (*a*) considerable, and in the case of tertiary alkylating agent complete, decomposition of the agent and (*b*) greater opportunity for the isomerisation of the agent. For example, *n*-propyl halide, *n*-propyl alcohol, and di-*n*-propyl ether severally in the presence of aluminium chloride effect only *iso*propylation of acetophenone; the product is 3-*iso*propylacetophenone.[2]

In general, alkylation of benzene with primary alkyl halide gives a mixture of primary and secondary alkylbenzene, and tertiary alkyl halide effects mainly secondary alkylation.[3] These generalisations do not apply to the corresponding intramolecular processes; these are comparatively fast and isomerisation is consequently less important. Thus each of the phenylalkyl chlorides, be it primary, secondary or tertiary, listed in Table 1 underoges ring closure without isomerisation.[1] The preparation of benzosuberane from 1-chloro-5-phenylpentane is noteworthy since this chloride is reported[4] as giving phenyl*cyclo*pentane.

These straightforward ring closures can no longer be effected after the reactivity of the phenyl group as a nucleophile has been decreased by acetylation.[1] Each of the chloroalkylacetophenones listed in Table 2 gives 5-acetyl-2-alkylindane on fusion with excess of aluminium chloride–sodium chloride at 100°. In each instance the final product is afforded by intramolecular primary alkylation; *i.e.*, it involves the most reactive alkylating agent and the least reversible process. The isomerisations of the chloroalkyl side-chains probably involve the following rearrangements :

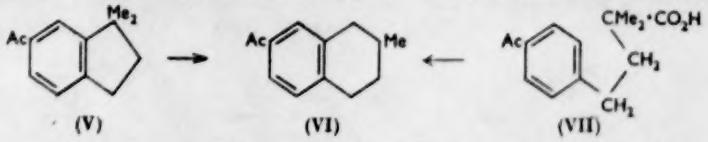
(i) $-CH_2\cdot CH_2\cdot CH_2Cl \longrightarrow -CH_2\cdot CHCl\cdot CH_3 \longrightarrow -CHCl\cdot CH_2\cdot CH_3$

as in (*D*) ⟶ (*E*) ⟶ (*F*) (see Table 2), a well-known phenomenon, and (ii) migration of a 4-acetylbenzyl group in the Wagner–Meerwein rearrangement of aralkyl cation as in (*B*) ⟶ (*C*) (see Table 2) :

Should ring closure be effected by tertiary alkylation the product would be unstable : it is shown [1] that 6-acetyl-1 : 1-dimethylindane (V) gives 7-acetyl-2-methyltetralin (VI), the same product as is afforded by αα-dimethyl-γ-*p*-acetylphenylbutyric acid (VII), by fusion with aluminium chloride.

[1] Unpublished work.
[2] Baddeley, *Quart. Rev.*, 1954, **8**, 355.
[4] Von Braun and Deutsch, *Ber.*, 1912, **45**, 1271, 2178.

Whereas the ketone (VI), like 6-acetyltetralin, is stable towards excess of aluminium chloride, alicyclic rings which are adjacent to an acetyl group in a benzene ring are readily



(V) (VI) (VII)

opened even when this process involves the formation of a primary alkyl cation. This instability is illustrated by the isomerisation of 9-acetyl-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-

TABLE 1.

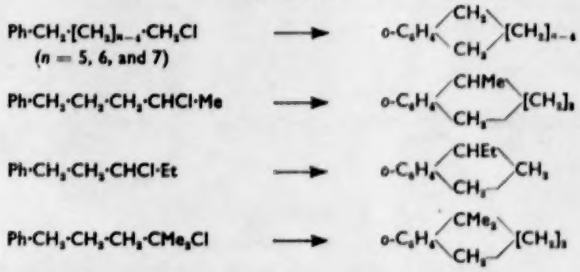


TABLE 2.

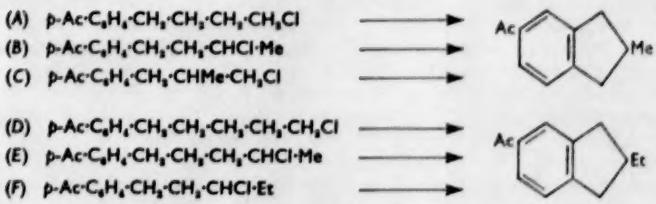
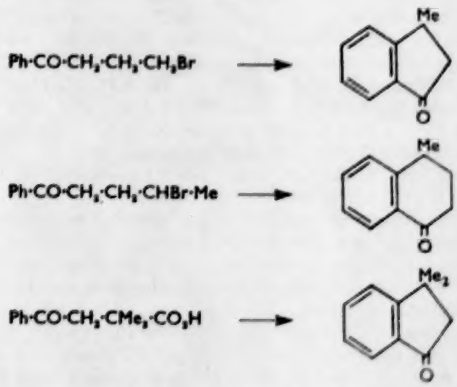


TABLE 3.

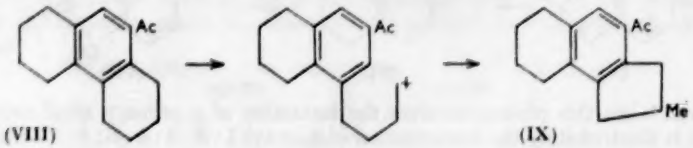


phenanthrene (VIII) ⟶ (IX) : [5] rupture of an alicyclic ring occurs and is followed by a series of rearrangements similar to those discussed above [Table 2, (*A*) ⟶ (*B*) ⟶ (*C*)]

[5] Baddeley and Pendleton, *J.*, 1952, 807.

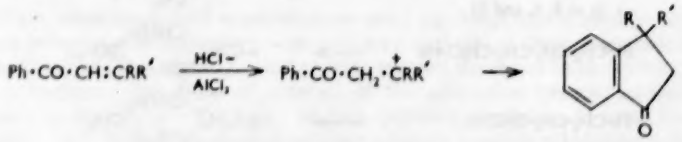
and reaction is completed by intramolecular primary alkylation with formation of a five-membered ring.

Ring closure of phenyl halogenoalkyl ketones occurs more readily than that of the above chloroalkylacetophenones : as shown by the data [1] in Table 3, it can be effected by intra-



(VIII) (IX)

molecular secondary and tertiary alkylation. These reactions are similar to those effecting ring closure of aryl vinyl ketones;[3] these compounds combine with a proton and then undergo intramolecular alkylation : *e.g.*,



Experimental

Intramolecular Acylations

Materials.—(i) *γ-p-Acetylphenylbutyric acid.* Ethyl γ-phenylbutyrate (30 g.) was gradually added to a mixture of aluminium chloride (90 g., 2 mol.) and acetyl chloride (25 g., 1 mol.) in ethylene chloride. When reaction was complete (15 min.) the mixture was decomposed with ice and dilute hydrochloric acid. Ethyl γ-*p*-acetylphenylbutyrate (30 g., 83%), b. p. 196—197°/12 mm., was obtained. It gave a *semicarbazone*, m. p. 188—189° (Found : C, 62·0; H, 7·4; N, 14·5. $C_{13}H_{21}O_3N_3$ requires C, 61·8; H, 7·2; N, 14·45%). Acid hydrolysis of the keto-ester gave the required *keto-acid* (22 g.) as needles, m. p. 53—54° (Found : C, 69·7; H, 6·9. $C_{12}H_{14}O_3$ requires C, 70·0; H, 6·8%). Attempts to prepare this compound by acetylation of γ-phenylbutyric acid gave α-tetralone (90%), identified by its oxime, m. p. and mixed m. p. 102—103°.

(ii) γ-p-*Carboxyphenylbutyric acid* was obtained from the above keto-acid by hypochlorite oxidation; it separated from water as needles, m. p. 194—195° (Found : C, 63·4; H, 5·8%; equiv., 101. $C_{11}H_{12}O_4$ requires C, 63·6; H, 5·8%; equiv., 104).

(iii) β-p-*Acetylphenylpropionic acid.* Methyl β-phenylpropionate (45 g.) in methylene chloride (100 ml.) was gradually added to a solution of aluminium chloride (100 g., 2·5 mol.) and acetyl chloride (100 g., 5 mol.) in methylene chloride (300 ml.). The brisk reaction gave *methyl* β-p-*acetylphenylpropionate* (52 g., 93%), b. p. 175°/12 mm. It gave a *semicarbazone*, m. p. 162—163° from methanol (Found : C, 58·9; H, 6·5; N, 15·5. $C_{13}H_{17}O_3N_3$ requires C, 59·3; H, 6·5; N, 16·0%). Acid hydrolysis of the keto-ester gave the required *keto-acid* (40 g.) which separated from water as long needles, m. p. 120° (Found : C, 68·7; H, 6·5%; equiv., 196. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·25%; equiv., 192).

(iv) Hypochlorite oxidation of the keto-acid gave β-*p*-carboxyphenylpropionic acid [6] which separated from water in needles, m. p. 284°.

(v) γ-p-*Acetylphenyl-αα-dimethylbutyric acid.* αα-Dimethyl-γ-phenylbutyric acid was obtained by Clemmensen reduction of the product of interaction of αα-dimethylsuccinic anhydride, aluminium chloride (2 mols.), and benzene (1·5 mols.) in ethylene chloride.[7] Its methyl ester (20 g.) in methylene chloride (50 c.c.) was gradually added to a solution of aluminium chloride (40 g., 3 mols.) and acetyl chloride (40 g., 5 mols.) in methylene chloride (150 c.c.). The rapid reaction gave methyl γ-*p*-acetylphenyl-αα-dimethylbutyrate (18 g.), b. p. 200°/12 mm. Its *semicarbazone* separated from methanol in needles, m. p. 193° (Found : C, 63·3; H, 7·4; N, 13·6. $C_{16}H_{23}O_3N_3$ requires C, 63·0; H, 7·5; N, 13·8%). Acid hydrolysis of the keto-ester gave the required *keto-acid* (16 g.), b. p. 196°/0·5 mm., needles (from light petroleum), m. p. 63° (Found : C, 71·4; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·7; H, 7·7%).

[6] Cf. Widman, *Ber.*, 1889, **22**, 2272.
[7] Cf. Rothstein and Saboor, *J.*, 1943, 425.

Cyclisations.—The above keto-acids and dicarboxylic acids were fused with aluminium chloride (5 mols.) and sodium chloride (1 mol.) at 180° for an hour. The reaction mixtures were decomposed with ice and hydrochloric acid and the products were isolated in the usual way.

(i) γ-*p*-Acetylphenylbutyric acid (3·6 g.) gave 7-*acetyl*-1-*tetralone* (2·5 g.) as needles, m. p. 67° (from light petroleum) (Found: C, 76·8; H, 6·4. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%). It was reduced by the Clemmensen method and catalytic dehydrogenation of the product gave 2-ethylnaphthalene (picrate, m. p. and mixed m. p. 77°).

(ii) γ-*p*-Carboxyphenylbutyric acid (1·6 g.) gave 7-*carboxy*-1-*tetralone* (0·5 g.), m. p. 216° (sealed tube), isolated by sublimation at 190—200°/0·2 mm. (Found: C, 69·5; H, 5·5%; equiv., 191. $C_{11}H_{10}O_3$ requires C, 69·4; H, 5·3%; equiv., 190). When reduced by the Clemmensen method, the product gave tetralin-6-carboxylic acid, m. p. and mixed m. p. 153°.

(iii) β-*p*-Acetylphenylpropionic acid gave 6-*acetylindan*-1-*one* which separated from light petroleum in needles, m. p. 98° (Found: C, 75·4; H, 5·70. $C_{11}H_{10}O_2$ requires C, 75·8; H, 5·75%). This compound combined with 2 : 4-dinitrophenylhydrazine (2 mol.), and the *product* separated from nitrobenzene in red needles, m. p. 310° (Found: C, 51·3; H, 3·4; N, 20·5. $C_{23}H_{18}O_8N_8$ requires C, 51·7; H, 3·4; N, 21·0%).

(iv) β-*p*-Carboxyphenylpropionic acid gave 6-*carboxyindan*-1-*one*, needles (from water), m. p. 256° (Found: C, 68·4; H, 4·2%; equiv., 178. $C_{10}H_8O_3$ requires C, 68·1; H, 4·55%; equiv., 176), and thence indane-5-carboxylic acid, m. p. and mixed m. p. 181°, by Clemmensen reduction.

(v) A mixture of γ-*p*-acetylphenyl-αα-dimethylbutyric acid (20 g.) and excess of aluminium and sodium chlorides decomposed at 140° with evolution of carbon monoxide and gave acetophenone (2 g.) (2 : 4-dinitrophenylhydrazone m. p. and mixed m. p. 237°), and 7-*acetyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*methylnaphthalene* (12 g.). Its *semicarbazone* separated from ethanol in needles, m. p. 196° (Found: C, 68·7; H, 7·8; N, 16·7. $C_{14}H_{19}ON_3$ requires C, 68·6; H, 7·8; N, 17·1%), and its 2 : 4-*dinitrophenylhydrazone* from ethyl acetate in red needles, m. p. 200—202° (Found: C, 61·5; H, 5·0; N, 15·1. $C_{19}H_{20}O_4N_4$ requires C, 61·9; H, 5·4; N, 15·2%). It gave 5 : 6 : 7 : 8-*tetrahydro*-7-*methyl*-2-*naphthoic acid*, needles, m. p. 138—140° (from water) (Found: C, 75·4; H, 7·4%; equiv., 192. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%; equiv., 190), when oxidised with alkaline hypochlorite. This acid was decarboxylated and dehydrogenated by palladium–charcoal in quinoline and gave 2-methylnaphthalene (picrate m. p. and mixed m. p. 115°).

Intramolecular Alkylation

Preparation of Phenylalkyl Halides and their p-*Acetyl Derivatives.*—(i) 1-Chloro-4-phenylbutane,[8] b. p. 120°/15 mm., (ii) 1-chloro-3-phenylbutane,[9] b. p. 100°/13 mm., (iii) 1-chloro-2-methyl-3-phenylpropane,[10] b. p. 101°/11 mm., (iv) 2-chloro-1-phenylpropane,[11] b. p. 98°/18 mm., (v) 1-chloro-5-phenylpentane,[12] b. p. 120°/12 mm., (vi) 4-chloro-1-phenylpentane, b. p. 100°/12 mm., and (vii) 3-chloro-1-phenylpentane, b. p. 100°/12 mm., were prepared from the corresponding alcohols by the action of thionyl chloride. 2-*Benzyl*-2-*chloropropane*, b. p. 92°/13 mm. (Found: Cl, 20·8. $C_{10}H_{13}Cl$ requires Cl, 21·0%), was prepared from 2-methyl-1-phenylpropan-2-ol by the combined action of concentrated hydrochloric acid and calcium chloride.

Friedel–Crafts acetylation of the aralkyl chlorides was attempted as follows: A solution of aluminium chloride (1·0 mol. as $AlCl_3$) in a mixture of acetyl chloride (1·5 mol.) and methylene chloride was gradually added to a stirred solution of the aralkyl chloride in methylene chloride. The reaction was over in a few nimutes and the mixture was decomposed with ice and hydrochloric acid. The organic layer was separated, washed with water, dried (Na_2SO_4), and distilled.

(i) 1-*p*-*Acetylphenyl*-4-*chlorobutane* (75% yield), b. p. 185—190°/12 mm., gave a 2 : 4-*dinitrophenylhydrazone* which separated from ethanol in orange-red needles, m. p. 144° (Found: Cl, 9·5; N, 14·3. $C_{18}H_{19}O_4N_4Cl$ requires Cl, 9·1; N, 14·3%). This chloro-ketone was also given by the action of concentrated hydrochloric acid and zinc chloride on the corresponding hydroxy-ketone, b. p. 160°/0·5 mm. [2 : 4-*dinitrophenylhydrazone*, m. p. 89° (Found: C, 57·6; H, 5·0; N, 15·2. $C_{18}H_{20}O_5N_4$ requires C, 58·1; H, 5·4; N, 15·1%)], which was obtained by the Friedel–Crafts acetylation of 4-phenylbutyl acetate.

(ii) 1-*p*-Acetylphenyl-3-chlorobutane, b. p. 175°/15 mm., was obtained in only 12% yield.

[8] Von Braun, *Ber.*, 1910, **43**, 2846.
[9] Von Braun and Neumann, *Ber.*, 1917, **50**, 53.
[10] Von Braun, Grabowski, and Kirschbaum, *Ber.*, 1913, **46**, 1278, 3041.
[11] Huston and Sager, *J. Amer. Chem. Soc.*, 1926, **48**, 1957.
[12] Ruzicka and Peyer, *Helv. Chim. Acta*, 1935, **18**, 676.

Its *semicarbazone* separated from ethanol in needles, m. p. 174° (Found: C, 58·8; H, 7·2; N, 15·3; Cl, 12·8. $C_{13}H_{18}ON_3Cl$ requires C, 58·3; H, 6·8; N, 15·7; Cl, 13·3%).

(iii) 1-*p*-Acetylphenyl-2-methyl-3-chloropropane (84% yield), b. p. 170°/12 mm., gave a *semicarbazone* which separated from ethanol in needles, m. p. 196° (Found: C, 57·9; H, 6·8; N, 15·2; Cl, 12·8. $C_{13}H_{18}ON_3Cl$ requires C, 58·3; H, 6·8; N, 15·7; Cl, 13·3%).

(iv) Attempts to acetylate 2-chloro-1-phenylpropane gave only non-volatile material.

(v) 1-*p*-Acetylphenyl-5-chloropentane (84% yield), b. p. 188°/12 mm., gave a *semicarbazone* which separated from ethanol in needles, m. p. 156° (Found: C, 60·4; H, 6·9; N, 15·4. $C_{14}H_{20}ON_3Cl$ requires C, 60·0; H, 7·1; N, 15·0%).

(vi) 1-p-*Acetylphenyl-4-chloropentane* (65% yield), b. p. 195°/23 mm. (Found: Cl, 15·6. $C_{13}H_{17}OCl$ requires Cl, 15·8%), was hydrolysed during its interaction with semicarbazide solution; the *product* did not contain chlorine and separated from ethanol in needles, m. p. 196° (Found: C, 68·4; H, 7·6; N, 15·8. $C_{14}H_{21}O_3N_3$ requires C, 68·8; H, 8·0; N, 16·0%).

(vii) 1-p-*Acetylphenyl-3-chloropentane* (50% yield), b. p. 190°/20 mm. (Found: Cl, 15·5. $C_{13}H_{17}OCl$ requires Cl, 15·8%), gave the *semicarbazone* of the corresponding hydroxy-ketone as needles, m. p. 192°, from ethanol (Found: C, 68·4; H, 7·7; N, 16·3. $C_{14}H_{21}O_3N_3$ requires C, 68·8; H, 8·0; N, 16·0%).

Cyclisation of Phenylalkyl Chlorides.—In each instance this was effected by addition of the organic chloride to a suspension of finely powdered aluminium chloride in light petroleum (b. p. 60—80°) and boiling the mixture under reflux for an hour.

1-Chloro-3-phenylpropane, 1-chloro-4-phenylbutane and 1-chloro-5-phenylpentane gave indane, tetralin, and benzosuberane respectively in 50% yield. These hydrocarbons were identified by the semicarbazones of their acetyl derivatives. Addition of the semicarbazone of *p-cyclo*pentylacetophenone (m. p. 216°) to that of 7-acetylbenzosuberane (m. p. 209°) depresses the m. p. of the latter (cf. ref. 4). 4-Chloro-1-phenylpentane gave 1 : 2 : 3 : 4-tetrahydro-1-methylnaphthalene (40%), b. p. 95°/12 mm., n_D^{20} 1·5285, which was dehydrogenated to 1-methylnaphthalene (picrate m. p. and mixed m. p. 140°) with palladium–charcoal at 280°. 3-Chloro-1-phenylpentane gave 1-ethylindane [12] (40%), b. p. 93°/12 mm., n_D^{20} 1·5235, whose 6-acetyl derivative gave a 2 : 4-*dinitrophenylhydrazone*, m. p. and mixed m. p. 154° (Found: C, 62·3; H, 5·4; N, 15·2. $C_{19}H_{20}O_4N_4$ requires C, 61·9; H, 5·4; N, 15·2%).

Cyclisation of p-*Acetylphenylalkyl Chlorides.*—This was effected by adding the chlorides to a stirred melt of aluminium chloride (5 parts) containing sodium chloride (10%) at 100°. The mixtures were stirred for an hour, then decomposed with ice and hydrochloric acid, and the products were isolated by distillation. Yields were 60—70%.

1-*p*-Acetylphenyl-4-chlorobutane, 1-*p*-acetylphenyl-3-chlorobutane and 1-*p*-acetylphenyl-2-methyl-3-chloropropane gave 5-acetyl-2-methylindane. Its 2 : 4-*dinitrophenylhydrazone* separated from ethanol in orange-red needles, m. p. and mixed m. p. 192° (Found: C, 60·6; H, 4·9; N, 15·6. $C_{18}H_{16}O_4N_4$ requires C, 61·0; H, 5·1; N, 15·9%). Authentic 5-acetyl-2-methylindane was obtained by acetylation of 2-methylindane.[13]

Cyclisation of the 5-, 4-, and 3-chloro-derivatives of 1-*p*-acetylphenylpentane gave 5-acetyl-2-ethylindane, b. p. 165°/20 mm., in each instance. An authentic sample was obtained by acetylation of 2-ethylindane.[14] Its *semicarbazone* separated from ethanol in needles, m. p. 215° (Found: C, 68·1; H, 7·7; N, 16·9. $C_{14}H_{19}ON_3$ requires C, 68·5; H, 7·8; N, 17·2%), and its 2 : 4-*dinitrophenylhydrazone* from acetic acid in orange-red needles, m. p. 186° (Found: C, 61·5; H, 5·5; N, 14·9. $C_{19}H_{20}O_4N_4$ requires C, 61·9; H, 5·5; N, 15·2%).

Preparation and Cyclisation of Bromoalkyl Phenyl Ketones.—(i) γ-Bromobutyrophenone (60 g.), b. p. 155—160°/15 mm., was obtained by adding a solution of γ-bromobutyryl chloride (80 g.) and aluminium chloride (60 g.) in methylene chloride (150 c.c.) to benzene (70 g., 2 mols.). It separated from light petroleum (b. p. 40°) in large plates m. p. 38—38·5° (Found: C, 53·1; H, 4·6; Br, 34·9. $C_{10}H_{11}OBr$ requires C, 52·8; H, 4·85; Br, 35·2%), and gave a 2 : 4-*dinitrophenylhydrazone* which separated from ethyl acetate in orange-red needles, m. p. 161° (Found: C, 47·5; H, 3·7; N, 13·4; Br, 19·3. $C_{16}H_{13}O_4N_4Br$ requires C, 47·1; H, 3·68; N, 13·75; Br, 19·65%).

(ii) γ-*Bromovalerophenone*, b. p. 150°/10 mm., was similarly prepared from γ-bromovaleryl chloride, as needles (from light petroleum), m. p. 26° (Found: C, 54·5; H, 5·5; Br, 32·7. $C_{11}H_{13}OBr$ requires C, 54·7; H, 5·4; Br, 33·2%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow-orange needles, m. p. 166—168° (Found: C, 48·7; H, 4·3; N, 13·5; Br, 18·5. $C_{17}H_{17}O_4N_4Br$ requires C, 48·5; H, 4·0; N, 13·3; Br, 19·0%).

[13] Plattner and Wyss, *Helv. Chim. Acta.*, 1941, **24**, 483.
[14] Wagner and Jauregg, *Ber.*, 1941, **74**, 1522.

The bromoalkyl phenyl ketones (10 g.) were cyclised by aluminium chloride (30 g.) and sodium chloride (4 g.) at 100° for an hour.

(i) γ-Bromobutyrophenone gave 3-methylindan-1-one [16] (4 g.), b. p. 120°/8 mm., identified by its semicarbazone, m. p. and mixed m. p. 230°, and by its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 240°.[15]

(ii) γ-Bromovalerophenone gave 4-methyl-1-tetralone (5 g.), b. p. 120—125°/8 mm., identified by its semicarbazone,[16] m. p. and mixed m. p. 210°, and by its 2 : 4-*dinitrophenylhydrazone*, orange plates, m.p. and mixed m. p. 216—217° (from ethyl acetate) (Found : C, 60·0; H, 4·8; N, 16·8. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%).

Fusion of β-Benzoyl-αα-dimethylpropionic Acid with Excess of Aluminium Chloride.—The keto-acid (10 g.) was gradually added to a stirred melt of aluminium chloride (30 g.) and sodium chloride (3 g.) at 140°. After an hour at 140° the mixture afforded initial keto-acid (3 g.) and 3 : 3-dimethylindan-1-one (4 g., 60%), b. p. 115—117°/18 mm. Its semicarbazone [17] separated from ethanol in needles, m. p. 205—207° (Found : C, 66·1; H, 6·7; N, 19·0. Calc. for $C_{12}H_{15}ON_3$: C, 66·4; H, 6·9; N, 19·3%), and its 2 : 4-*dinitrophenylhydrazone* from ethyl acetate in red needles, m. p. 266° (Found : C, 60·1; H, 4·6; N, 16·0. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%). Clemmensen reduction of the ketone gave 1 : 1-dimethylindane which was identified as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 212°, of its 6-acetyl derivative.

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[16] Marvel, Dee, and Cooke, *J. Amer. Chem. Soc.*, 1940, **62**, 3499, 3503.
[15] Meyer and Stamm, *Ber.*, 1923, **56**, 1424.
[17] Von Auwers, *Ber.*, 1921, **54**, 994.

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891. *The Reaction of Tetra-alkylammonium Halides with Potassium in Liquid Ammonia.*

By D. A. HAZLEHURST, A. K. HOLLIDAY, and G. PASS.

The cation of a tetra-alkylammonium salt NR_4X undergoes N–C bond fission with potassium in liquid ammonia, giving a hydrocarbon RH and an amine NR_3. With a tetramethylammonium salt the yield of methane decreases in the order X = Cl, Br, I, and C–H fission may occur to yield hydrogen and ethylene. The rate of reaction at −78° is R = Pr^n > Me > Et; unsymmetrical ions R_3NMe^+ react very rapidly, yielding methane. Amide ion resulting from N–C fission or solvolysis gives olefin if R contains a β-carbon atom.

THE reaction of tetramethylammonium iodide with a solution of potassium in liquid ammonia was first investigated by Thompson and Cundall; [1] the products at room temperatures were trimethylamine, ethane, and potassium iodide. Schlubach and Ballauf [2] found that tetraethylammonium chloride and potassium yielded more gas than that expected from the equation $2K + 2NEt_4Cl = 2KCl + 2NEt_3 + C_4H_{10}$. Recently, Jolly [3] has found that tetraethylammonium bromide and potassium in liquid ammonia at −36° yield triethylamine and variable amounts of ethylene, ethane, and hydrogen. In some of Jolly's experiments, ferric nitrate was added to catalyse the reaction between the ammoniated electron (written as e^- here) and solvent, *i.e.*, $2e^- + 2NH_3 = 2NH_2^- + H_2$. It is known that the reaction of the ions NEt_4^+ and NH_2^- yields ethylene, and it is not clear how much of Jolly's ethylene was formed in this way.

One object of all the above investigations was to find evidence for the existence of the tetra-alkylammonium radical NR_4. In the reaction $NR_4X + K$ (X = halogen), in liquid ammonia, KX is precipitated; hence there are in solution NR_4^+ ions and solvated electrons, e^-. The latter may undergo solvolysis to give amide ion and hydrogen; or they may unite with the NR_4^+ ions to give radicals NR_4; or they may attack NR_4^+ ions and break bonds.

[1] Thompson and Cundall, *J.*, 1888, **53**, 761.
[2] Schlubach and Ballauf, *Ber.*, 1921, **54**, 2811.
[3] Jolly, *J. Amer. Chem. Soc.*, 1955, **77**, 4958.

Valency considerations make the existence of the radical NR_4 seem improbable, and hence breakdown of the ion NR_4^+ is likely; Birch [4] has shown that electrons of metal–ammonia solutions can produce fission of the N–C bonds in quaternary ammonium ions (*e.g.*, $Ph{\cdot}NMe_3^+ \longrightarrow PhH + NMe_3$). Kantor and Hauser [5] have shown that fission of a C–H bond can occur by reaction of a base B^- (*e.g.*, NH_2^-) in liquid ammonia, *e.g.*,

$$R_3\overset{+}{N}{\cdot}\overset{|}{C}H + NH_2^- \longrightarrow NH_3 + R_3\overset{+}{N}{\cdot}\overset{|}{\bar{C}}- \quad (I)$$

The carbanion (I) may then re-arrange to give a tertiary amine, or undergo alkylation. If a β-carbon atom with attached hydrogen is present, then β-elimination is preferred, giving an olefin, *e.g.*,

$$R_3\overset{+}{N}{\cdot}CH_2{\cdot}CH_3 + NH_2^- \longrightarrow R_3N + C_2H_4 + NH_3$$

In the present work, the reaction of NR_4^+ ions and ammoniated electrons has been investigated *in vacuo* at −78°, and as many reaction products as possible have been analysed quantitatively so that the reaction mechanism might be understood.

Experimental

All manipulations involving liquid ammonia were made in a vacuum apparatus. The ammonia was dried over sodium and stored as gas. Quaternary ammonium halides were either obtained from B.D.H. or made by usual methods; they were dried *in vacuo* and analysed for purity before use. The dry salt was introduced into the reaction tube, followed by the potassium (weighed under light petroleum), and the tube was then attached to the vacuum system and pumped for some hours. About 10 c.c. of liquid ammonia were condensed into the tube, and the latter was sealed off and left at −78°, with occasional shaking, until the blue colour disappeared. The tube was then placed in liquid nitrogen and opened to the vacuum system; non-condensable gases were removed with the Töpler pump and analysed by combustion. The ammonia was carefully removed from the reaction tube, and condensable hydrocarbon products were then separated by fractionation through U-traps; absorption of the large amount of ammonia on calcium chloride assisted separation of hydrocarbons of similar vapour pressure to ammonia. Condensable and non-condensable hydrocarbon products were analysed by combustion, by absorption in bromine water, and by infrared absorption spectra; vapour-density measurements were also made in some cases. Identification of the small amount of amine formed (<0·1 g.) in presence of much ammonia was carried out by one or more of the following methods: (*a*) allowing amine to accumulate in the solvent ammonia from successive experiments and then extracting the hydrochloride with chloroform (Watt and Otto's method [6]); (*b*) using larger quantities of reactants, and then separating the amines by fractional distillation, using the micro-still described by Craig; [7] (*c*) separating the hydrochlorides by paper chromatography.[8]

After removal of all volatile material from the reaction tube, the solid residue was dissolved in water, warmed to remove any traces of ammonia and amine, and analysed for (i) alkalinity (corresponding to amide ion content of the residue), (ii) potassium and quaternary ammonium ion concentration, by use of sodium tetraphenylboron, and (iii) halide content, as a check on the amount of salt added initially. From (ii) and (iii) the amount of quaternary salt used in the reaction could be estimated. Determinations in the residues were occasionally precluded by loss of solid on removal of solvent ammonia.

Results.—These are given in Tables 1, 2, and 3; units are mmoles unless otherwise stated. Expts. 1—7, Table 1, were with potassium and tetraethylammonium chloride. The results of expts. 1 and 2 show that very variable ethane : ethylene ratios were obtained under apparently similar conditions, and that the time of reaction (*i.e.*, the time to become colourless) also varied. It may be noted that solutions of potassium with no quaternary salt present became colourless after very variable periods of time, and that these times were of the same order as those obtained

[4] Birch, *Quart. Reviews*, 1950, **4**, 69.
[5] Kantor and Hauser, *J. Amer. Chem. Soc.*, 1951, **73**, 4122.
[6] Watt and Otto, *ibid.*, 1947, **69**, 836.
[7] Craig, *Ind. Eng. Chem. Anal.*, 1936, **8**, 219.
[8] Schwyzer, *Acta Chem. Scand.*, 1952, **6**, 219.

when tetraethylammonium chloride was present. In expts. 3 and 4 excess of potassium was used but similar variations occurred; the use of excess of quaternary salt (expt. 5) or of a higher reaction temperature (expt. 6) did not produce any significant changes except that the reaction time was much shorter at the higher temperature. In expt. 7, the reaction tube was opened after a short period of reaction to find the relative rates of production of ethane and

TABLE 1.

Experiment	1	2	3	4	5	6	7	8†	9†
Temp.	−78°	−78°	−78°	−78°	−78°	−33°	−78°	−78°	−78°
NEt_4Cl added	1·00	1·06	1·06	0·55	2·15	1·03	1·05	1·10	1·28
NEt_4Cl used	—	—	1·06	0·55	1·00	—	—	0·75	1·19
K added	0·92	0·99	3·96	1·45	1·08	0·92	0·94	0·91	1·16
Products: H_2	0·03	0·27	1·38	0·60	0·05	—	0·01	0·00	0·00
C_2H_6	0·45	0·22	0·48	0·12	0·54	0·42	0·08	0·00	0·00
C_2H_4	0·45	0·66	0·55	0·39	0·55	0·46	0·06	0·29	1·04
NH_2^-	—	0·08	—	0·87	0·05	—	—	0·61	0·08
Time (hr.)	120	186	230	160	160‡	20	6*	24	168

* Reaction incomplete.
† Potassium–ammonia solution colourless before addition of NEt_4Cl.
‡ Left at −78° for a further 384 hours.

TABLE 2.

Experiment	10	11	12	13	14†	15†
Halide (X)	Cl	Cl	Br	I	Cl	Cl
NMe_4X added	1·32	6·26	1·48	1·17	2·62	1·92
,, used	0·56	0·70	—	0·27	0·03	0·51
K added	1·14	1·35	1·31	1·15	1·94	1·10
Products: H_2	0·06	0·23	0·34	0·35	0·00	0·00
CH_4	0·49	0·44	0·03	0·20	0·00	0·00
C_2H_6/C_2H_4	trace	trace	trace	trace	0·06*	0·00
NH_2^-	0·54	0·78	—	0·79	1·81	0·54
Time (hr.)	45	41	168	140	44	312

* Ethylene only.
† Potassium–ammonia solution colourless before addition of NMe_4Cl.

TABLE 3.

Experiment	16	17	18	19	20	21
Cation	$Pr^n_4\overset{+}{N}$	$Et_3\overset{+}{N}H$	$Et_3\overset{+}{N}Me$	$Et_3\overset{+}{N}Me$	$Pr^n_3\overset{+}{N}Me$	$Pr^n_3\overset{+}{N}Me$
added	1·56	1·37	1·36	1·32	1·43	1·32
used	0·98	—	1·07	0·94	1·43	1·00
K added	1·07	1·17	1·07	0·96	1·16	1·12
Products: H_2	0·02	0·54	0·00	0·02	0·00	0·00
CH_4	0·00	0·00	0·45	0·38	0·34	0·52
C_2H_6	0·00	0·00	trace	trace	trace	trace
C_2H_4	0·00	0·00	0·42	0·40	0·00	0·00
C_3H_8	0·48	0·00	0·00	0·00	0·00	0·00
C_3H_6	0·52	0·00	0·00	0·00	0·45	0·47
NH_2^-	0·15	0·07	0·11	0·10	0·28	0·10
Amines	Pr^n_3N	Et_2N	Et_3N	Et_3N	Pr^n_3N	Pr^n_3N
Found	—	—	Et_2NMe	Et_2NMe	Pr^n_2NMe	Pr^n_2NMe
Time (hr.)	<20	<0·01	4	4	0·6	1·6

ethylene. In expts. 8 and 9, the reaction was between potassium amide and tetraethylammonium chloride, and the reaction times were arbitrary. Ethylene was the only hydrocarbon product of these amide reactions.

In the above experiments, triethylamine was the only amine product identified, and no higher hydrocarbons or methane was found.

The results of potassium–tetramethylammonium halide reactions are given in Table 2, expts. 10—13. Methane was the major hydrocarbon product, and trimethylamine was the only amine identified. The trace of noncondensable hydrocarbon was found (in expt. 10) to be mainly ethane, containing a little olefin, probably ethylene. In expts. 10 and 11, with the chloride, the effect of increasing the concentration of the latter was to increase the hydrogen yield, but there was little change in reaction time. Expts. 12 and 13 show that the hydrocarbon yield was reduced when the bromide and iodide were used. In expts. 14 and 15,

potassium amide was used and the reaction times were arbitrary. Expt. 14 (where a little ethylene was found) was a single experiment, whereas 15 is typical of several similar experiments in which no ethylene was found.

The reaction of tetra-*n*-propylammonium chloride and potassium is given as expt. 16, Table 3. The other results in this table are for unsymmetrical quaternary salts. The reaction with trimethylammonium chloride was very rapid and hydrogen was the only gaseous product. Triethylmethylammonium chloride also reacted fairly rapidly, and reproducible results were obtained; little or no hydrogen was formed and there were two amine products as well as methane, ethylene, and a trace of ethane. Expts. 20 and 21, by use of methyltri-*n*-propylammonium chloride gave similar results, and propylene instead of ethylene.

Discussion

From a quaternary ion NR_4^+, the hydrocarbon RH and the amine NR_3 are always obtained. This clearly indicates N–C bond fission as postulated by Birch,[4] and suggests the scheme

$$NR_4^+ + e^- \longrightarrow NR_3 + R \quad . . . . . (1)$$

$$R + e^- \longrightarrow R^- \quad . . . . . (2)$$

$$R^- + NH_3 \longrightarrow RH + NH_2^- \quad . . . . . (3)$$

Amide ion is also produced by electron solvolysis, *i.e.*,

$$NH_3 + e^- \longrightarrow NH_2^- + \tfrac{1}{2}H_2 \quad . . . . . (4)$$

The tetraethylammonium ion reacts slowly, and the variation in ethane : ethylene ratio does not appear to be determined by reactant ratio or temperature. The absence of butane suggests that ethyl radicals formed by reaction (1) immediately undergo reaction (2), so that disproportionation of ethyl radicals is unlikely as a source of ethylene. The latter must be formed by the reaction

$$NEt_4^+ + NH_2^- \longrightarrow NEt_3 + C_2H_4 + NH_3 \quad . . . . . (5)$$

If amide ion were formed only by (3), then equal amounts of ethane and ethylene would be expected—provided that reaction (5) is complete when the solution becomes colourless. The results of expts. 8 and 9 verify reaction (5), but show that the reaction is slow at −78°. Expt. 7 shows that formation of ethylene is somewhat less than that of ethane at an early stage in the reaction, and expt. 5 shows that while a $C_2H_6 : C_2H_4$ ratio may exceed 1 after 160 hr. or so, the ultimate ratio is 1 after long storage, *i.e.*, when reaction (5) is complete. But there are experiments in which the $C_2H_6 : C_2H_4$ ratio is much less than 1, and here more ethylene must be formed by amide from the solvolysis reaction (4). The solvolysis reaction can proceed at a rate comparable with that of the ethane-forming reaction; but this rate is subject to considerable variation because of the possible presence of a trace of catalyst. Hence, if the solvolysis reaction happens to be catalysed, then extra ethylene and hydrogen are produced at the expense of ethane. The stoicheiometric basis for this reasoning can be understood by reference to expt. 2. Here, 0·22 mmole of C_2H_4 was produced by amide from reaction (3); hence 0·44 mmole must have been produced by amide from the solvolysis reaction. This corresponds to 0·22 mmole of hydrogen, but the amount actually found was 0·27 mmole. Hence $0{\cdot}05 \times 2 = 0{\cdot}10$ mmole of amide was produced, by solvolysis, in excess of that used to produce ethylene, and should have remained as such. In fact 0·08 mmole was found in the residue. A similar check can be applied in the other cases where the data are available. In expt. 2, the potassium required to produce ethane and ethylene was 0·44 mmole, for the " excess " of ethylene 0·44 mmole, and as residual amide 0·08 mmole, a total of 0·96 mmole compared with 0·99 mmole actually added.

Tetramethylammonium chloride (Table 2) reacts more rapidly than the tetraethylammonium salt, and any effect of solvolysis is therefore reduced. However, the results show that the yield of methane is reduced and that of hydrogen increased by using the bromide or iodide, or by using a large excess of the chloride (expt. 11). Now the amount of

quaternary salt added in these experiments exceeds that required to saturate the liquid ammonia at −78°. The effective concentration of quaternary ion is therefore determined primarily by the extent to which the anion X^- is removed as insoluble KX; and as the solubilities of KX are in the order KI > KBr > KCl, the quaternary-ion concentration (and yield of methane) will be low in the case of the bromide and iodide. The unused electrons in these cases take part in slow solvolysis and the hydrogen yield therefore increases. The amount of methane and hydrogen is satisfactorily accounted for by the equations (1)—(4). Thus, in expt. 10, 0·98 mmole of potassium is required for the methane and 0·12 mmole for the hydrogen, *i.e.*, 1·10 mmoles. The remainder of the potassium added (0·04 mmole) can be accounted for in terms of the trace of condensable hydrocarbon, mainly ethane. The latter may originate by combination of two methyl radicals, from reaction (1), or by a reaction

$$NMe_4^+ + Me^- \longrightarrow NMe_3 + C_2H_6 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Porter [9] has shown that methyl radicals are produced from tetramethylammonium amalgam on heating, and the recovery of ethane from Thompson and Cundall's tetramethylammonium iodide–potassium reaction at ordinary temperature [1] suggests that radical combination may have occurred in their experiments. But reaction (6) is also a possible source of ethane, since the CH_3^- ion acts as a base in liquid ammonia and so can attack the quaternary ion. In the case of tetraethylammonium salts no corresponding reaction to give butane occurred, probably because of preferential attack on the NEt_4^+ ion by NH_2^- rather than by $C_2H_5^-$ ions.

The results of Table 2 show that some amide and quaternary ions have reacted, but without giving hydrocarbon products. Franklin [10] refers to a reaction

$$NMe_4^+ + NH_2^- \longrightarrow [NMe_4{\cdot}NH_2] \longrightarrow NMe_3 + Me{\cdot}NH_2$$

and the results of expt. 15 show that this reaction occurs slowly at −78°. There remains the single experiment 14, where a small amount of ethylene was produced from the NMe_4^+–NH_2^- reaction, and the probability that a trace of ethylene was formed in the NMe_4^+–K reactions also. Formation of ethylene would require, first, fission of a C–H bond by a base B^-, thus : [5]

$$Me_3\overset{+}{N}{\cdot}Me + B^- \longrightarrow Me_3\overset{+}{N}{\cdot}\bar{C}H_2 + BH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The carbanion formed by this reaction has been prepared in ether solution by Wittig and Wetterling.[11] They found it to be stable; it did not rearrange to give ethyldimethylamine, nor did it decompose directly to give ethylene. Reaction with water gave tetramethylammonium hydroxide. Hence, if ethylene is to be formed from this carbanion, it must be by alkylation to $Me_3N^+{\cdot}CH_2Me$ followed by β-elimination. Now if the base B^- in reaction (7) is NH_2^-, then the reaction produces ammonia. In liquid ammonia as solvent, the reverse of reaction (7) seems probable, by analogy with the reaction with water. Hence little or no ethylene would be expected from a NMe_4^+–NH_2^- reaction. But if B^- is identified as e^-, then reaction (7) becomes

$$\overset{+}{N}Me_4 + e^- \longrightarrow Me_3\overset{+}{N}{\cdot}\bar{C}H_2 + \tfrac{1}{2}H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and hydrogen is produced : and if the carbanion is then destroyed by ammonia, the other reaction product is amide, so that the overall result is

$$e^- + NH_3 \longrightarrow NH_2^- + \tfrac{1}{2}H_2$$

i.e., the same as the solvolysis reaction. It is therefore possible that carbanion formation by reaction (8) can yield a trace of ethylene by alkylation, but the greater amount of carbanion must undergo solvolysis and produce amide. In expt. 11, a large excess of

[9] Porter, *J.*, 1954, 760.
[10] Franklin, "The Nitrogen System of Compounds," Reinhold, New York, 1935, p. 63.
[11] Wittig and Wetterling, *Annalen*, 1947, **557**, 193.

tetramethylammonium chloride produced more hydrogen and amide, and less hydrocarbon, than the normal amount. It may be that the production of amide and hydrogen was here catalysed by the carbanion mechanism; equally, the effect may have been a heterogeneous catalysis of the solvolysis reaction by the large amount of undissolved quaternary salt.

The reaction of tetra-*n*-propylammonium chloride and potassium (expt. 16, Table 3) proceeds rapidly and little solvolysis occurs. Propane and propene are found in approximately equal amounts as would be expected if amide ion formed by reaction (3) reacts completely with the $Pr^n_4N^+$ ion to yield propene. However, the latter reaction is not complete, since some amide and unchanged quaternary ion are found in the residues. It is therefore possible that all the propane formed was not recovered from the ammonia, *i.e.*, the ratio propane : propene is too low.

The rate of reaction of tetra-alkylammonium ions and potassium is in the order R = Pr^n > Me > Et. The rapid reaction of the tetrapropylammonium ion may be attributed to two factors—the greater solubility of the quaternary salt, and the greater ease of fission of the N–Pr bond compared with that of N–Et or N–Me. The more rapid reaction of tetramethyl- than of tetraethyl-ammonium ion cannot be attributed to these factors; but it may well be that reactions (2) and (3) occur more readily with methyl than with ethyl radicals.

With the unsymmetrical quaternary ions of Table 3, N–H or N–C fission occurred to give the tertiary amine, *i.e.*, hydrogen was obtained from trimethylammonium ions and methane from triethyl- or tri-*n*-propyl-methylammonium ions. The amide produced attacks the group with a β-carbon atom if available, *i.e.*,

$$Et_3NMe^+ + NH_2^- \longrightarrow Et_3NMe + C_2H_4 + NH_3$$
$$Pr^n_3NMe^+ + NH_2^- \longrightarrow Pr^n_3NMe + C_3H_6 + NH_3$$

so that two amines are formed in the products. The order of ease of fission here is H > Me > larger alkyl, and the rapidity of reaction of the unsymmetrical ions may be due to a combination of steric effects, the presence of an easily removed hydrogen atom or methyl group, and the ready occurrence of reactions (2) and (3). The appearance of a trace of ethane from the ions Et_3NMe^+ and $Pr^n_3NMe^+$ is of interest. Formation by a reaction

$$R_3NMe^+ + Me^- \longrightarrow R_3N + C_2H_6$$

is unlikely, since methyl ions undergo rapid solvolysis; and in any case, the Me^- ion is a base and the reaction would therefore be (for Et_3NMe^+)

$$Et_3NMe^+ + Me^- \longrightarrow Et_3NMe + MeH + C_2H_4$$

It is more likely that ethane is formed here by union of methyl radicals since these will be released more readily from triethyl- or tripropyl-methylammonium than from tetramethylammonium ions.

Thanks are due to Professor G. E. Coates for some helpful suggestions, and to Mr. P. Kennedy for assistance with some of the experimental work. One of us (G. P.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant.

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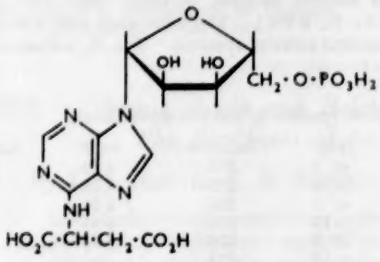
892. *Synthesis of "6-Succinoaminopurine" [6-(1 : 2-Dicarboxyethylamino)purine].*

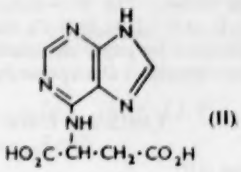
By J. Baddiley, J. G. Buchanan, F. J. Hawker, and J. E. Stephenson.

2 : 6 : 8-Trichloropurine with aspartic acid at pH 9 gives the dichloroaminopurine (III) in good yield. Removal of the two chlorine atoms with phosphine and hydrogen iodide yields the aminopurine (II), identical with a substance obtained by acid hydrolysis of a nucleotide (I) which had been produced enzymically from fumarate and adenosine-5′ phosphate.

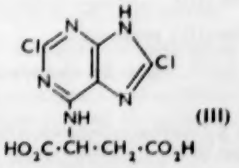
The unusual purine nucleotide (I) was first isolated by Carter and Cohen [1] as a product of the reaction between adenosine-5′ phosphate and fumarate in the presence of an enzyme isolated from a yeast autolysate. It is also formed from inosine-5′ phosphate and aspartate in the presence of an enzyme from *Escherichia coli*,[2] and probably occupies a central position in the important conversion of inosine-5′ phosphate into adenosine-5′ phosphate.[2,3] Acid hydrolysis of the nucleotide yields "6-succinoaminopurine" [6-(1 : 2-dicarboxyethylamino)purine] (II). Since the identification of this and the original nucleotide depends largely on ultraviolet absorption spectra and chromatographic properties,[4] we considered that a synthesis of the purine (II) was desirable.



(I)



(II)



(III)

A convenient starting material for the synthesis of 6-substituted purines is 2 : 6 : 8-trichloropurine. This is readily prepared from uric acid,[5] and the 6-chlorine atom is replaced by an amino-group under moderate reaction conditions.[6] The chlorine atoms in 6-amino-2 : 8-dichloropurine have been removed by reduction with phosphonium iodide and hydrogen iodide, and in related glycosides catalytic methods have been used.[7]

2 : 6 : 8-Trichloropurine was heated in aqueous solution at pH 9 with aspartic acid and the resulting dichloro-aminopurine (III) was isolated in good yield by acidification. The absorption spectrum of this compound was similar to that of the purine (II) and its nucleotide (see Table 1). Attempts to remove the chlorine atoms catalytically were unsuccessful: it is possible that the acidic hydrogen atom at position 9 or 7 may prevent the correct orientation of the molecule and catalyst.

The two chlorine atoms were replaced by hydrogen when phosphine was passed through a suspension of the compound in hydrogen iodide. The product (II) was isolated in about 30% yield by chromatography on a Dowex-2 column. It was indistinguishable from a sample kindly provided by Dr. C. E. Carter when examined by paper chromatography

[1] Carter and Cohen, *J. Amer. Chem. Soc.*, 1955, **77**, 499.
[2] Lieberman, *ibid.*, 1956, **78**, 251.
[3] Abrams and Bentley, *ibid.*, 1955, **77**, 4179.
[4] Carter, personal communication.
[5] Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 2936.
[6] Fischer, *Ber.*, 1897, **30**, 2226.
[7] Davoll, Lythgoe, and Todd, *J.*, 1948, 967.

in several solvent systems, and the ultraviolet absorption spectra were identical. On electrometric titration it consumed approximately two equivalents of alkali.

The pyrimidine ring in this compound and its nucleotide is somewhat unstable towards acids.[4] After hydrolysis for several hours in 0·5N-hydrochloric acid at 100°, 5-aminoglyoxaline-4-carboxyamide was detected among the products from the synthetic purine and from the sample provided by Dr. Carter, being identified by paper chromatography. It absorbed ultraviolet light on the paper and gave characteristic colours when sprayed with diazotised sulphanilic acid or nitrous acid followed by β-naphthol in dilute alkaline solution.

Experimental

2 : 6 : 8-*Trichloropurine*.—This was prepared as its ammonium salt by the method of Davoll and Lowy [5] without modification. Although the ammonium salt was reasonably stable, the free purine slowly evolved hydrogen chloride.

2 : 8-*Dichloro*-6-(1 : 2-*dicarboxyethylamino*)*purine*.—The ammonium salt of 2 : 6 : 8-trichloropurine (3·0 g., 1 mol.) and DL-aspartic acid (3·36 g., 2 mols.) were dissolved in hot water (75 ml.). Sodium hydroxide was added to pH 9, followed by sodium carbonate (1·61 g., 1·2 mols.), and the solution was refluxed for 9 hr. Concentrated hydrochloric acid was added to the cooled solution until a permanent precipitate had been formed. The mixture was kept at 0° overnight and the resulting precipitate (2·17 g., 60%) was filtered off, washed with water, and dried (P_2O_5 and KOH). The slight colour was removed (charcoal) during recrystallisation from hot water. The 2 : 8-*dichloro-compound* formed needles, decomp. 220—225° (Found : C, 34·4; H, 2·6. $C_9H_7O_4N_5Cl_2$ requires C, 33·8; H, 2·2%). The substance was homogeneous when examined by paper chromatography in several solvent systems. For R_F values see Table 2, and for ultraviolet absorption data see Table 1.

TABLE 1. *Ultraviolet absorption spectra of purine derivatives.*

	pH	$\lambda_{max.}$ (mμ)	log ε	$\lambda_{min.}$ (mμ)
Purine (III)	< 1	272·5	4·30	236
	>12	279·5	4·32	245
Purine (II) : synthetic	< 1	275	4·24	235
	>12	274	4·24	240
from Dr. Carter's data	< 1	276	4·25	235
	>12	275	—	244

6-(1 : 2-*Dicarboxyethylamino*)*purine*.—A stream of nitrogen was passed for 1 hr. through a suspension of the dichloro-purine (500 mg.) in hydriodic acid (20 ml.; freshly distilled from red phosphorus; b. p. 126°; *d* 1·7). Phosphine (from 6 g. of white phosphorus and 8 g. of sodium hydroxide in 100 ml. of water) was diluted with nitrogen, and the mixed gases were passed through a condenser (to remove some water), then through sulphuric acid, and into the purine in hydriodic acid at 70°. After 2 hr. the dark brown mixture was evaporated to dryness below 50° and the residue was dissolved in water (100 ml.). Most of the iodine was removed by continuous extraction with carbon disulphide. The disulphide reservoir contained a saturated solution of sodium arsenite to prevent volatilisation of the extracted iodine. The aqueous layer was evaporated to about half its volume below 40° to remove carbon disulphide, water was added (to 500 ml.), and the solution was adjusted to pH 4·5 with ammonia.

The purine was isolated from the above solution by chromatography on a Dowex-2 (formate form) resin column (205 ml.; 200—400 mesh). After absorption of reaction products, the column was washed with water (500 ml.) and eluted with 0·5M-formic acid. Fractions (25 ml.) were collected automatically, the product being detected by optical density at 276 mμ. It was the first substance to be eluted and was usually contained in about 200 ml. Appropriate fractions were bulked and evaporated to dryness below 40°. The resulting gum was dried at the oil-pump and then dissolved in water (10 ml.). The solution was concentrated (to 2 ml.) and acetone (10 ml.) was added, whereupon the product (57 mg.) crystallised. Concentration of the mother-liquors and addition of acetone gave a further crop (73 mg.) of less well-crystallised material (total yield 33%). This *purine* may be recrystallised with some loss from aqueous acetone. It does not melt but chars at 190° and evolves gas at 225° (Found : C, 42·5; H, 3·9. $C_9H_9O_4N_5$ requires C, 43·0; H, 3·6%). On electrometric titration with 0·01N-sodium hydroxide it consumed approx. 2 equivs. up to pH 7 (Found : equiv., 124·8. $\frac{1}{2}C_9H_9O_4N_5$ requires equiv., 125·5).

Acid Hydrolysis.—A solution of the foregoing material (3·8 mg.) in 0·5N-hydrochloric acid (0·1 ml.) was heated in a sealed tube in a boiling-water bath for 5 hr. Solvent was removed in a desiccator, and the products were examined by paper chromatography in solvent system *D* (see below). The aminoglyoxaline derivative had R_F 0·66 and was identified by comparison with an authentic sample on an adjacent track. Its presence was demonstrated by absorption of ultraviolet light and by the dark blue colour produced when the paper was sprayed with a dilute solution of diazotised sulphanilic acid in sodium hydrogen carbonate. A second paper was exposed to nitrous fumes and then sprayed with a 1% solution of β-naphthol in 1% sodium hydroxide solution. The glyoxaline gave an orange colour on the paper.

Paper Chromatography.—Ascending-front chromatography on Whatman No. 4 paper was used. The following solvent systems were used: *A*, *iso*propyl alcohol–water–ammonia (*d* 0·88) (3 : 2 : 1); *B*, *n*-butyl alcohol–acetic acid–water (2 : 1 : 1); *C*, *n*-butyl alcohol–acetic acid–water (4 : 1 : 5) (organic layer); *D*, *n*-propyl alcohol–ammonia (*d* 0·88)–water (6 : 3 : 1); *E*, 5% disodium hydrogen phosphate solution–*iso*pentyl alcohol (2 : 1). Results are in Table 2.

TABLE 2. *R_P values in solvent systems A—E.*

	A	*B*	*C*	*D*	*E*
Purine (III)	0·81	0·83	0·82	0·45	0·85
Purine (II)	0·76	0·61	0·45	0·29	0·86

We thank the Department of Scientific and Industrial Research for a Maintenance Allowance held by one of us (J. E. S.).

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893. *Tetronic Acids and Related Compounds. Part II.* The Synthesis of (±)-Carolinic Acid.*

By L. J. HAYNES, J. R. PLIMMER, and (in part) A. H. STANNERS.

Use of ethoxymagnesiomalonic ester in place of sodiomalonic ester gives improved yields in Benary's method for the synthesis of tetronic acids. This modification is used in the condensation of ethyl β-oxoadipate and α-chloropropionyl chloride to give, after cyclisation and hydrolysis of the product, (±)-carolinic acid. Condensation of γ-bromobutyryl chloride with ethoxymagnesiomalonic ester gives diethyl tetrahydro-2-furylidenemalonate (III).

THE mould *Penicillium Charlesii* G. Smith, when grown on a nutrient medium containing glucose, produces among other products a number of tetronic acid derivatives,[1] the structures of which were established by degradation.[2] Of these products, only γ-methyltetronic acid (I; R = H) had hitherto been synthesised, and it seemed desirable to confirm the structure of a more typical member, *e.g.*, carolinic acid (I; R = $CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$), by synthesis.

Anschütz[3] and Benary[4] prepared ethoxycarbonyltetronic acids by condensing α-acetoxy- or α-halogeno-acyl halides with an excess of ethyl sodiomalonate and cyclisation of the product *in situ*. We have improved this approach by the use of ethyl ethoxymagnesiomalonate,[5] and have thus prepared α-ethoxycarbonyltetronic, α-ethoxycarbonyl-γ-phenyltetronic, and (±)-carolinic acid.

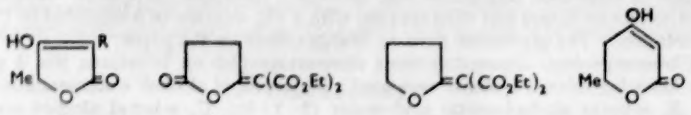
Equimolecular amounts of chloroacetyl chloride and ethyl ethoxymagnesiomalonate gave α-chloroacetylmalonic ester in good yield: this was cyclised when kept at room temperature or heated, giving α-ethoxycarbonyltetronic acid. In this cyclisation the yields are not good, although this route is a considerable improvement in ease and in yield on

* Part I, *J.*, 1956, 4103.

[1] Clutterbuck, Haworth, Raistrick, Smith, and Stacey, *Biochem. J.*, 1934, **28**, 94.
[2] Clutterbuck, Raistrick, and Reuter, *ibid.*, 1935, **29**, 300.
[3] Anschütz and Bertram, *Ber.*, 1903, **36**, 468; Anschütz and Böcker, *Annalen*, 1909, **368**, 53.
[4] Benary, *Ber.*, 1907, **40**, 1079; 1911, **44**, 1759.
[5] Lund, *Ber.*, 1934, **67**, 935.

Benary's. Reaction of acetylmandelyl chloride with ethyl ethoxymagnesiomalonate gave a 65% overall yield of γ-phenyltetronic acid, whereas with ethyl sodiomalonate the overall yield was 48%.

Reaction of the ethoxymagnesio-derivative of ethyl β-oxoadipate [6] in benzene with α-chloropropionyl chloride and subsequent hydrolysis gave crude ethyl 6-chloro-4-ethoxycarbonyl-3 : 5-dioxo-octanoate as an oil which cyclised to ethyl carolinate on standing for



(I) (II) (III) (VI)

some weeks or when heated at 120°/25 mm. Alkaline hydrolysis gave (±)-carolinic acid, m. p. 137·5° [cf. (+)-carolinic acid, m. p. 123°], identical with the natural acid in ultraviolet absorption and behaviour on paper chromatography and to ferric chloride. It formed a 2 : 4-dinitrophenylhydrazone, m. p. 228° [(+)-isomer, m. p. 228°].

In preliminary experiments on the analogous synthesis of carolic acid (I; R = $CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH$), we condensed ethoxymagnesiomalonic ester with γ-bromobutyryl chloride in the hope that this would lead to the carolic acid side chain. However, instead of the expected product $CH_2Br{\cdot}[CH_2]_2{\cdot}CO{\cdot}CH(CO_2Et)_2$, a solid compound, $C_{11}H_{16}O_5$, was obtained. On acid hydrolysis this gave γ-butyrolactone. The compound gave no colour with ferric chloride solution and had an absorption maximum at 2470 Å (ε 13,800). Ruggli and Maeder [7] have shown that reaction of succinoyl chloride or succinic anhydride with sodiomalonic ester gives the $\Delta^{1:2}$-enol lactone (II), and we consider that our product is diethyl tetrahydro-2-furylidenemalonate (III) formed by cyclisation with loss of hydrogen bromide from the enolic form of the expected bromo-compound. In agreement with this suggestion, condensation of diethyl ethoxymagnesioethylmalonate with γ-bromobutyryl chloride gave the expected ester (IV) which did not cyclise, either to a furan derivative or to a seven-membered analogue of a tetronic acid. It was hydrolysed by dilute aqueous-ethanolic potassium hydroxide at room temperature, to yield ethylmalonic acid. These findings led us to prepare the chloro-ester (V) : this showed no tendency to cyclise, even when kept for two years. Cyclisation of the bromo-compound (IV) to a seven-membered ring analogue of a tetronic acid may be regarded as unlikely; but the cyclisation of the chloro-compound (V) should lead to the lower homologue of the six-membered ring analogue (VI) of tetronic acid which has been prepared [8] from 5-hydroxyhex-2-ynoic acid [9] and is known to show properties similar to those of tetronic acid, so it seems that the cyclisation which leads to a tetronic acid from an α-substituted γ-halogenoacetoacetic ester depends on activation of the halogen atom by an adjacent carbonyl group.

Experimental

α-Ethoxycarbonyltetronic Acid.—Dry ethanol (25 ml.) and carbon tetrachloride (0·5 ml.) were added to magnesium (5 g.). When the vigorous reaction had subsided, more ethanol (11 ml.) was added and the mixture heated under reflux for 1 hr. Next morning redistilled diethyl malonate (33·7 g.) was added and dissolution of the magnesium completed by heating the mixture on a water-bath for 1 hr. The resulting complex was dissolved in dry ether and the solution cooled in ice. Chloroacetyl chloride (25 g.) in dry ether (17 ml.) was added during 1 hr., the mixture heated under reflux for 30 min., then cooled to 0°, and the complex decomposed, first, with ice and then with dilute sulphuric acid. The ether layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*, to leave a yellow oil (30 g.) (Found : Cl, 14·3%). Distillation of a sample gave diethyl malonate, b. p. 85°/10 mm., and then *diethyl chloroacetylmalonate*, b. p.

[6] Macdonald, *J.*, 1952, 4176; Eisner, Elvidge, and Linstead, *J.*, 1950, 2223; Riegel and Lilienfield, *J. Amer. Chem. Soc.*, 1945, **67**, 1274.
[7] Ruggli and Maeder, *Helv. Chim. Acta*, 1943, **26**, 1476, 1499; 1944, **27**, 436.
[8] Jones and Whiting, *J.*, 1949, 1419.
[9] Haynes and Jones, *J.*, 1946, 503.

130—133°/10 mm., n_D^{19} 1·4648 (Found: Cl, 15·0. $C_9H_{13}O_5Cl$ requires Cl, 15·0). Only small quantities of this compound could be obtained as decomposition occurred during the distillation with the formation of solid α-ethoxycarbonyltetronic acid.

The crude chloro-compound (25 g.) in xylene (30 ml.) was heated under reflux for 2 hr. Addition of light petroleum (b. p. 40—60°) precipitated α-ethoxycarbonyltetronic acid (7·5 g.), m. p. 125° (from ethyl acetate) (Benary [4] gives m. p. 124—125°).

α-Ethoxycarbonyl-γ-phenyltetronic Acid.—Diethyl malonate (40 g.) in dry ether (100 ml.) was added during 30 min. to a suspension of magnesium ethoxide (from magnesium, 6·08 g.) in ether. The mixture was heated under reflux for 30 min. and set aside overnight. Excess of ethanol was then removed by azeotropic distillation with toluene, and the resulting green syrupy complex was dissolved in dry ether (150 ml.). *O*-Acetylmandelyl chloride [10] (53 g.) in dry ether (60 ml.) was added with stirring to the solution at such a rate that the solvent refluxed gently. When the addition was nearly complete an insoluble greenish-white complex separated. The mixture was set aside overnight, then heated on a water-bath for 30 min. The complex was decomposed by ice and then sulphuric acid (17 ml. of concentrated acid diluted with water to 40 ml.). The ether layer was separated and the aqueous layer extracted with ether. The ethereal solutions were combined, dried (Na_2SO_4), and evaporated *in vacuo*. The residual yellow oil (91 g.) was dissolved in aqueous 4N-sodium hydroxide (250 ml.) and set aside for 3 days. Addition of an excess of sulphuric acid precipitated α-ethoxycarbonyl-γ-phenyltetronic acid (42·5 g.) containing a little γ-phenyltetronic acid. Recrystallisation from ethyl acetate or ethanol gave the ethoxycarbonyl compound as prisms, m. p. 145° (Anschütz and Böcker [3] give m. p. 140°).

γ-Phenyltetronic Acid.—The above crude α-ethoxycarbonyl-γ-phenyltetronic acid (20 g.) was boiled under reflux with aqueous 2N-sodium hydroxide (100 ml.) for 45 min. Addition of concentrated hydrochloric acid precipitated a cream-coloured solid; recrystallisation of this from water gave γ-phenyltetronic acid (13·5 g.), m. p. 127° (Anschütz and Böcker [3] give m. p. 127·5—128·5°). Its 2 : *4-dinitrophenylhydrazone* had m. p. 137° (from ethanol) (Found: C, 53·5; H, 3·8; N, 15·6. $C_{16}H_{12}O_8N_4$ requires C, 53·5; H, 3·4; N, 16·2%).

O-*Acetyl-γ-phenyltetronic Acid.*—(*a*) γ-Phenyltetronic acid (2 g.) was heated with *iso*propenyl acetate (10 ml.) and 3 drops of 10% methanolic 2 : 5-dichlorobenzenesulphonic acid on a water-bath for 30 min., then set aside overnight. Volatile material was evaporated *in vacuo*. The remaining dark brown oil slowly solidified. Extraction with boiling light petroleum (b. p. 40—60°) and recrystallisation from the same solvent gave O-*acetyl-γ-phenyltetronic acid* as needles, m. p. 79·5° (Found: C, 65·8; H, 4·6. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%).

(*b*) γ-Phenyltetronic acid (1·5 g.), treated with acetic anhydride (4 ml.) and a drop of concentrated sulphuric acid, gave *O*-acetyl-γ-phenyltetronic acid, m. p. and mixed m. p. 79°.

2-(*4-Acetonyl-2 : 5-dihydro-2-oxo-5-phenyl-3-furyl*)-2-(2 : *5-dihydro-4-hydroxy-2-oxo-5-phenyl-3-furyl*)*propane* (cf. ref. 11).—A solution of γ-phenyltetronic acid (2 g.) in acetone (60 ml.) containing 2 drops of piperidine was refluxed during 2 hr. The excess of acetone was evaporated under reduced pressure. The residual gum solidified on treatment with ether. The solid was ground with a little ethyl acetate, and the colourless residue collected. Recrystallisation from ethanol gave the *isopropylidene compound* as prisms m. p. 177° (Found: C, 72·1; H, 5·7. $C_{34}H_{34}O_8$ requires C, 72·2; H, 5·6%). The substance gave a red colour with ferric chloride.

(±)-*Carolinic Acid.*—Ethyl β-oxoadipate [6] (16 g.) was added to a solution of magnesium ethoxide (from 1·75 g. of magnesium) in dry benzene (50 ml.): when the vigorous reaction had subsided the solution was evaporated under reduced pressure to remove ethanol, leaving a green syrupy residue. (±)-α-Chloropropionyl chloride (9·5 g.) in dry benzene (25 ml.) was added slowly to a solution of the syrup in dry benzene; no immediate reaction was observed but a green viscous complex separated when the solution was warmed. The mixture was refluxed for 2 hr., left overnight, cooled to 0°, and treated with ice-water and then dilute sulphuric acid. The benzene layer was separated and the aqueous layer extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue, crude ethyl 6-chloro-4-ethoxycarbonyl-3 : 5-dioxo-octanoate, was a pale yellow oil which gave an orange-red colour with ferric chloride. When this compound was kept for some weeks or heated at 120°/25 mm. for 3 hr., its chlorine content dropped to zero, showing that cyclisation had taken place. The crude cyclised product (10 g.) was set aside in 2% aqueous sodium hydroxide (200 ml.) for 48 hr. at room temperature. The solution

[10] Thayer, *Org. Synth.*, Coll. Vol. I, 1st edn., p. 12.
[11] Wolff and Schlimpff, *Annalen*, 1901, **315**, 151.

was extracted with ether to remove unhydrolysed material and then acidified to pH 3 with dilute hydrochloric acid. Extraction with ether gave a small amount of β-oxoadipic acid (0·1 g.). The aqueous residue was then continuously extracted with ether during 24 hr. Evaporation of the dried (Na_2SO_4) extract gave crude (±)-carolinic acid, m. p. 116°, which recrystallised from ethyl acetate as prisms, m. p. 137·5° [Found: C, 50·45; H, 4·75%; equiv., 113. Calc. for $C_9H_{10}O_4$: C, 50·45; H, 4·7%; equiv. (dibasic), 107]. Both the synthetic and the natural acid gave orange colours, stable to concentrated hydrochloric acid, with ferric chloride. They showed identical R_F's on paper chromatography with use of the solvent systems: ethanol–ammonia (*d* 0·880)–water (20 : 1 : 4 v/v), R_F 0·49; butanol–acetic acid–water (4 : 1 : 5 v/v), R_F 0·50; propanol–ammonia (*d* 0·880)–water (2 : 1 : 1 v/v), R_F 0·60.

The 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way and recrystallised from nitrobenzene–toluene, had m. p. 228—229° (decomp.) (Found: C, 46·7; H, 3·75; N, 13·9. $C_{15}H_{14}O_8N_4$ requires C, 45·7; H, 3·6; N, 14·2%). Clutterbuck, Raistrick, and Reuter [8] give m. p. 228° (decomp.) for (+)-carolinic acid 2 : 4-dinitrophenylhydrazone.

Diethyl Tetrahydro-2-furylidenemalonate (III).—γ-Bromobutyryl chloride [12] (135 g.) in dry ether (100 ml.) was added with stirring during 5 hr. to a solution of diethyl methoxymagnesiomalonate [from magnesium (24 g.) and diethyl malonate (160 g.)] in dry ether (300 ml.). A viscous yellow complex separated. The mixture was set aside for 48 hr., then hydrolysed at 0° with dilute sulphuric acid. The ether layer was separated, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Distillation of the residual oil (176 g.) gave a forerun of diethyl malonate, b. p. *ca.* 45°/0·1 mm., and then a fraction (110 g.), b. p. 129°/0·1 mm., which solidified. After recrystallisation from light petroleum (b. p. 40—60°) the product, *diethyl tetrahydro-2-furylidenemalonate*, had m. p. 52·5—54° (Found: C, 58·0; H, 6·9; Br, 0. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%). It was readily soluble in organic solvents and insoluble in water; it gave no colour with ferric chloride in aqueous ethanol and reduced aqueous potassium permanganate. Light absorption in EtOH: $\lambda_{max.}$ 2470 Å (ε 14,000).

The ester (5 g.) was refluxed for 1 hr. with 2N-sulphuric acid (50 ml.). The solution was then saturated with ammonium sulphate and extracted with ether. Isolation by the usual procedure gave γ-butyrolactone (1 g.), identified as the derived phenylhydrazide, m. p. and mixed m. p. 93—94° (Seib [13] gives m. p. 93·7—94°).

Diethyl 7-Bromo-4-oxoheptane-3 : 3-dicarboxylate.—γ-Bromobutyryl chloride (186 g.) in dry ether (75 ml.) was added dropwise with stirring during 2½ hr. to a solution of diethyl ethoxymagnesioethylmalonate [from magnesium (24 g.) and diethyl ethylmalonate (188 g.)] in dry ether (500 ml.). Stirring was continued for a further 4 hr. and the mixture then set aside for 36 hr. Hydrolysis with dilute sulphuric acid gave a light brown liquid (290 g.) which on distillation gave diethyl ethylmalonate and then the *diester* (173 g.), b. p. 119°/0·02 mm., $n_D^{17.5}$ 1·4694 (Found: C, 47·4; H, 6·6. $C_{18}H_{31}O_8Br$ requires C, 46·2; H, 6·3%). Light absorption in EtOH: $\lambda_{max.}$ 2470 Å (ε 1500). The compound gave no colour with ferric chloride.

The bromo-compound (11 g.) was set aside for 2 days in 1 : 1 aqueous-ethanolic 5% potassium hydroxide (150 ml.) and then acidified with 2N-sulphuric acid (150 ml.). Isolation by the usual procedure gave ethylmalonic acid (3 g.), m. p. 110—112° (lit.,[14] m. p. 111°) (di-*p*-nitrobenzyl ester, m. p. 72—73°; lit.,[15] m. p. 75·2°).

Diethyl 4-Chloro-2-oxobutane-1 : 1-dicarboxylate.—β-Chloropropionyl chloride (64 g.) in dry ether (75 ml.) was added dropwise with stirring during 2 hr. to a solution of methoxymagnesiomalonic ester [from magnesium (12 g.) and diethyl malonate (80 g.)] in ether (200 ml.). A yellow-brown viscous complex separated. The mixture was set aside for 1 hr. Hydrolysis with dilute sulphuric acid gave the *diester* (85 g.), b. p. 106—109°/0·3 mm., $n_D^{21.5}$ 1·4672 (Found: C, 47·6; H, 6·1; Cl, 14·7. $C_{10}H_{15}O_5Cl$ requires C, 47·9; H, 6·0; Cl, 14·2%). Light absorption in EtOH: $\lambda_{max.}$ 2600 Å (ε 9300).

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[12] McElvain and Carney, *J. Amer. Chem. Soc.*, 1946, **68**, 2599; Henry, *Bull. Soc. chim. France*, 1886, **46**, 65.
[13] Seib, *Ber.*, 1927, **60**, 1399.
[14] Markownikoff, *Annalen*, 1876, **182**, 332.
[15] Lyman and Reid, *J. Amer. Chem. Soc.*, 1917, **39**, 705.

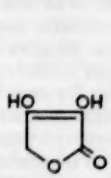
894. *Tetronic Acids and Related Compounds. Part III.** *The Claisen Ester Condensation of Ethyl Tetrahydro-2-pyranyloxyacetate.*

By L. J. Haynes and J. R. Plimmer.

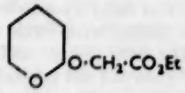
The Claisen ester condensation of benzoylglycollic ester has been employed for the preparation of α-hydroxytetronic acid (I) by Micheel and Jung.[1] However, it seemed likely that improved yields and a cleaner reaction might be obtained by protection of the hydroxyl group of glycollic ester as its dihydropyran adduct,[2] and we now report an examination of this route.

Ethyl tetrahydro-2-pyranyloxyacetate (II) was prepared in good yield by reaction of ethyl glycollate with 2 : 3-dihydropyran in presence of a trace of hydrochloric acid or when an acid ion-exchange resin [Amberlite IR-120 (H)] was used as catalyst. The product was characterised as the amide.

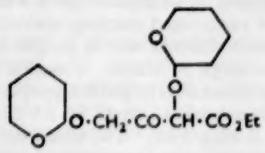
The ester reacted smoothly with sodium and a trace of ethanol in ether to give a syrup which could not be distilled under ordinary conditions without decomposition, but by short-path distillation yielded ethyl αγ-di(tetrahydro-2-pyranyloxy)acetoacetate (III)



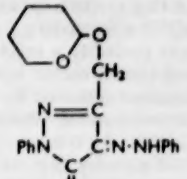
(I)



(II)



(III)



(IV)

which gave a lilac colour with ferric chloride solution and had $\lambda_{max.}$ 2620 Å (ε 700) in ethanol, shifted to longer wavelengths by addition of sodium ethoxide. The crude product also contained a slightly lower-boiling material which gave a red-brown colour with ferric chloride and a purple colour, indicative of an ene-diol system, with saturated aqueous *o*-dinitrobenzene followed by a few drops of alkali.[3] It was presumably ethyl α-hydroxy-γ-tetrahydropyranyloxy- or γ-hydroxy-α-tetrahydropyranyloxy-acetoacetate formed by hydrolysis, but was not examined further. The bistetrahydropyranyl ester was characterised by the formation of a derivative with phenylhydrazine. The bright orange product was expected to be the corresponding pyrazolone, but its molecular formula, $C_{21}H_{22}O_3N_4$, suggests that it has the structure (IV).

Hydrolysis of the ester (III), first with dilute sulphuric acid to remove the tetrahydropyranyl groups and then with concentrated hydrochloric acid, gave a brown syrup which in one experiment crystallised. On paper chromatography this syrup showed as a single spot (2 : 6-dichlorophenolindophenol spray) in the position expected for hydroxytetronic acid. It gave hydroxytetronic acid bisphenylhydrazone on treatment with phenylhydrazine.

Alkaline hydrolysis of the ester (III) gave the expected 1 : 3-di(tetrahydro-2-pyranyloxy)acetone as an oil.

Experimental.—Ethyl tetrahydro-2-pyranyloxyacetate. (*a*) One drop of concentrated hydrochloric acid was added to a mixture of redistilled 2 : 3-dihydropyran (29·5 g.) and ethyl glycollate (19·5 g.). The temperature rose rapidly but was kept below 40° by cooling. The mixture was set aside for 3 hr., a few pellets of potassium hydroxide were added to remove the acid, and the liquid was distilled under reduced pressure. *Ethyl tetrahydro-2-pyranyloxyacetate* (30 g., 80%)

* Part II, preceding paper.

[1] Micheel and Jung, *Ber.*, 1933, **66**, 1291; 1934, **67**, 1660.

[2] Paul, *Bull. Soc. chim. France*, 1934, **1**, 971; Woods and Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246.

[3] Fearon and Kawerau, *Biochem. J.*, 1943, **37**, 326.

was thus obtained as a liquid, b. p. 73°/0·4 mm., n_D^{16} 1·4440 (Found : C, 57·4; H, 8·4. $C_9H_{16}O_4$ requires C, 57·4; H, 8·5%).

(*b*) Amberlite IR-120(H) ion-exchange resin (0·5 g., dried) was added to a mixture of redistilled 2 : 3-dihydropyran (17 g.) and ethyl glycollate (10 g.). The temperature rose slowly from 22° to 26°. The mixture was kept for 20 hr. at room temperature, then filtered, and the filtrate was distilled as before. The yield of adduct was 12·2 g. (70%).

The *amide* was prepared by treatment of the ester with an excess of ammonia solution (*d* 0·880) overnight. It crystallised after removal of solvent under reduced pressure and recrystallised from benzene as prisms, m. p. 66·5° (Found : C, 53·0; H, 8·2; N, 8·7. $C_7H_{13}O_3N$ requires C, 52·8; H, 8·2; N, 8·8%).

Ethyl αγ-di(tetrahydro-2-pyranyloxy)acetoacetate. Ethyl tetrahydropyranyloxyacetate (20 g.) in dry ether (20 ml.) was added to sodium wire (2·7 g.) in dry ether (200 ml.) whilst a stream of dry nitrogen was passed through the liquid. The mixture was left at room temperature for 24 hr., the sodium slowly dissolving with slight effervescence and a yellow sodio-derivative separating. The reaction was completed on the water-bath (1 hr.). A little ethanol was then added to destroy unchanged sodium, and the mixture was then cooled to 0°, treated with ice and aqueous tartaric acid, and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated under reduced pressure. The red-brown oil when distilled in a short-path distillation apparatus gave three main fractions : (i) b. p. 75—98°/0·05 mm., $n_D^{18\cdot5}$ 1·4620 (2·47 g.); (ii) b. p. 98—113°/0·05 mm., $n_D^{18\cdot5}$ 1·4674 (1·70 g.); and (iii) b. p. 113—122°/0·05 mm., $n_D^{18\cdot5}$ 1·4730 (1·70 g.). Fraction (i) in ethanol gave a red-brown colour with ferric chloride and was probably a mixture of unchanged starting material and fraction (ii). Fraction (ii) gave a red-brown colour with ferric chloride and a purple colour on addition of aqueous *o*-dinitrobenzene followed by a few drops of alkali. Fraction (iii) was *ethyl αγ-di(tetrahydro-2-pyranyloxy)acetoacetate* which in ethanol slowly gave a purple-lilac colour with ferric chloride (Found : C, 57·8; H, 8·0. $C_{16}H_{26}O_7$ requires C, 58·2; H, 7·9%). The ester (0·5 g.) and phenylhydrazine (0·5 g.) were kept at 100° during 1 hr. The resultant red gum did not crystallise on treatment with light petroleum but after chromatography on alumina formed orange prisms, m. p. 123° (Found : C, 66·7; H, 5·8; N, 14·4. $C_{21}H_{22}O_3N_4$ requires C, 66·7; H, 5·8; N, 14·8%), presumably 4 : 5-*dioxo*-1-*phenyl*-3-(*tetrahydro*-2-*pyranyloxymethyl*)*pyrazolidine*-4-*phenylhydrazone* (IV).

Acid hydrolysis of ethyl αγ-di(tetrahydro-2-pyranyloxy)acetoacetate. Hydroxytetronic acid bisphenylhydrazone. The ester (2·85 g.) and 0·2N-sulphuric acid (10 ml.) were shaken in an inert atmosphere during 3 days. Sulphuric acid was removed by addition of the theoretical amount of 0·1N-barium hydroxide, and the solution was freeze-dried. A pale yellow oil remained. This was kept for 20 hr. in concentrated hydrochloric acid (2 ml.) and water (2 ml.). Solvent was then removed over potassium hydroxide *in vacuo*. The residue was a brown gum : in one experiment the gum crystallised partly but could not be recrystallised. A sample of the gum was examined by paper chromatography with butan-1-ol–glacial acetic acid–water (4 : 1 : 5) as the solvent system, and ascorbic acid as a reference compound, the paper being subsequently sprayed with a solution of 2 : 6-dichlorophenolindophenol. Ascorbic acid had R_F 0·39 and the gum gave a single spot at R_F 0·66. Mapson and Partridge [4] give ascorbic acid R_F 0·37, hydroxytetronic acid R_F 0·63. The gum (0·5 g.) was left at room temperature with phenylhydrazine (1·5 g.) and a drop of glacial acetic acid for 48 hr. Hydroxytetronic acid bisphenylhydrazone (0·7 g.) separated as a red solid which on recrystallisation from ethanol had m. p.s 168° and 215° (decomp.) (Found : C, 65·3; H, 5·0; N, 19·1. Calc. for $C_{16}H_{14}O_3N_4$: C, 65·30; H, 4·7; N, 19·1%). Micheel and Jung [1] give m. p.s 180° and 238°.

Alkaline hydrolysis of ethyl αγ-di(tetrahydro-2-pyranyloxy)acetoacetate. 1 : 3-*Di(tetrahydro-2-pyranyloxy)acetone.* The ester (4·5 g.) was kept in aqueous-methanolic sodium hydroxide (1·0 g. in 100 ml. of methanol and 10 ml. of water) for 24 hr. Water (100 ml.) was added, the solution was extracted several times with ether, and the ether extract dried (Na_2SO_4) and evaporated under reduced pressure. The residual pale yellow oil on short-path distillation gave 1 : 3-*di(tetrahydro-2-pyranyloxy)acetone*, b. p. 85—90° (bath-temp.)/0·01 mm., $n_D^{17\cdot5}$ 1·4748 (Found : C, 60·6; H, 8·5. $C_{13}H_{22}O_5$ requires C, 60·4; H, 8·5%).

We thank Professor E. L. Hirst for advice and encouragement, and Trinity College, Dublin, for the award of a John Winthrop Hackett prize (to J. R. P.).

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[4] Mapson and Partridge, *Nature*, 1949, **164**, 479.

895. 4-*Benzoyldiphenylamine.*

By M. P. Lippner and Muriel L. Tomlinson.

Plant and Worthing [1] found that benzoyl groups could not be introduced into the benzene nuclei of diphenylamine by the Friedel–Crafts method. 4-Benzoyldiphenylamine has now been made by the Chapman rearrangement of *p*-benzoylphenyl *N*-phenylbenzimidoate.

Experimental.—p-*Benzoylphenyl N-phenylbenzimidoate.* Benzanilide (9·8 g.), dried at 100° for 5 hr., was suspended in dry toluene (50 c.c.) and treated with phosphorus pentachloride (10·42 g.). After being heated at 100° until evolution of hydrogen chloride ceased (1 hr.), the colourless solution formed was evaporated under reduced pressure. The resulting *N*-phenylbenzimidoyl chloride, which solidified, was dissolved in dry ether (40 c.c.) and filtered slowly into a solution made by adding *p*-hydroxybenzophenone (10·1 g.) to absolute ethanol (50 c.c.) in which sodium (1·9 g.) had been previously dissolved. Sodium chloride separated, and, after storage overnight in a stoppered vessel, the solvents were removed by distillation and the resulting oil was thoroughly washed with water, extracted with ether, and dried ($MgSO_4$). When the ether had been distilled, the residue solidified after prolonged cooling and rubbing with ethanol. p-*Benzoylphenyl N-phenylbenzimidoate* (8·3 g., 82%) separated from ethanol as colourless prisms, m. p. 98—99° (Found: C, 83·1; H, 5·0. $C_{26}H_{19}O_2N$ requires C, 82·8; H, 5·0%).

4-*Benzoyldiphenylamine.* *p*-Benzoylphenyl *N*-phenylbenzimidoate (8 g.) was heated for 40 min. at 270—280°; the melt was cooled and formed a brown glass which crystallised when rubbed with alcohol. N: 4-*Dibenzoyldiphenylamine* (7·2 g., 90%) separated from ethanol as colourless prisms, m. p. 138° (Found: C, 83·0; H, 5·2. $C_{26}H_{19}O_2N$ requires C, 82·8; H, 5·0%). Hydrolysis with aqueous-alcoholic potassium hydroxide (1 hr.) afforded 4-*benzoyldiphenylamine* (4·7 g., 89%), which crystallised from ethanol as yellow plates, m. p. 155° (Found: C, 83·4; H, 5·4. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5%). It formed a 2:4-*dinitrophenylhydrazone* (red prisms), m. p. 196° (Found: C, 66·2; H, 4·2. $C_{25}H_{19}O_4N_5$ requires C, 66·2; H, 4·4%). Treatment of a solution of 4-benzoyldiphenylamine in acetic acid with 1 equiv. of aqueous sodium nitrite gave 4-*benzoyl-N-nitrosodiphenylamine*, m. p. 82°, as yellow prisms (from methanol) (Found: C, 75·8; H, 4·7. $C_{19}H_{14}O_2N_2$ requires C, 75·5; H, 4·6%). *N-Acetyl-4-benzoyldiphenylamine* was obtained by boiling 4-benzoyldiphenylamine with acetic anhydride for 5 hr. It crystallised from ethanol as prisms, m. p. 119—120° (Found: C, 80·1; H, 5·4. $C_{21}H_{17}O_2N$ requires C, 80·0; H, 5·4%).

The Dyson Perrins Laboratory, Oxford University. [*Received, July 12th,* 1956.]

[1] Plant and Worthing, *J.*, 1955, 1278.

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896. *Carbamoylglyoxaline.*

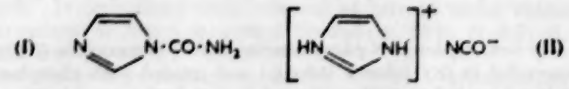
By J. M. Lowenstein.

Mixing a solution of potassium cyanate with a neutralized solution of glyoxaline yields a precipitate which might be carbamoylglyoxaline (I) or glyoxalinium cyanate (II). We show below that the former structure is correct.

A saturated solution of the compound was prepared by stirring an excess of it with water at 0° for 10 minutes and filtering off the undissolved solid. One drop of 1% aqueous cobaltous nitrate, added to 0·2 ml. of such a solution, freshly prepared, gave a very pale grey colour which changed rapidly to a deep blue colour if the solution was boiled. The blue colour also developed if the solution was kept at room temperature overnight. When the cobalt reagent was added to a day-old solution of the compound or to an aqueous solution of potassium cyanate of comparable amount and concentration, the blue colour was at once formed. Glyoxaline itself gave a pink colour and the solution became turbid when boiled. (Ammonium chloride and urea also gave no blue colour, in the cold or when boiled.)

1 ml. of 2N-nitric acid was added to 0·2 ml. of a freshly prepared solution of carbamoylglyoxaline. There was no immediate liberation of gas; from a day-old solution carbon dioxide was liberated immediately. Under similar conditions potassium cyanate liberated carbon dioxide immediately.

The infrared absorption spectrum of the compound, in a potassium bromide disc, did not show the strong absorption maximum of 4·55 μ characteristic of the cyanate ion.



The chemical tests and the spectrum indicate the absence, or virtual absence, of free cyanate and this is interpreted as support for structure (I). The chemical tests indicate further that the compound decomposes in water, probably *via* the cyanate (II). From the mode of synthesis and decomposition it may be assumed that there is an equilibrium in aqueous solution of the type carbamoylglyoxaline ⇌ glyoxalinium cyanate.

Citrulline is formed enzymically from carbamoyl phosphate and ornithine.[1] Potassium cyanate can replace carbamoyl phosphate in this reaction. The rate of reaction with potassium cyanate is stimulated by the addition of orthophosphate. This indicates that potassium cyanate first forms carbamoyl phosphate, which then reacts in the usual manner. Carbamoylglyoxaline can also replace carbamoyl phosphate in the enzymic formation of citrulline from ornithine. The rate of its reaction is also stimulated by the addition of orthophosphate (see Table), which suggests that carbamoylglyoxaline affords carbamoyl phosphate, which then reacts in the usual manner. Since either compound (I) or (II) might act in this way, the experiments cannot be taken as evidence for either structure, but the results are of interest from the point of view of possible enzyme mechanisms.

Addition	Citrulline formed (μmole)
None	0·01
Enzyme + phosphate	0·02
Carbamoylglyoxaline	0·07
Carbamoylglyoxaline + enzyme	0·27
Carbamoylglyoxaline + enzyme + phosphate	3·69
Potassium cyanate	0·02
Potassium cyanate + enzyme	0·40
Potassium cyanate + enzyme + phosphate	6·24

Experimental.—Carbamoylglyoxaline. Glyoxaline (3·40 g.) was dissolved in 2N-hydrochloric acid (17 ml.). The solution had pH ~7 (external indicator). A solution of potassium cyanate (4·06 g.) in water (5 ml.) was added at 20°. A heavy white precipitate formed after 4—5 min. The mixture was stirred for 1 hr. at 20°, then filtered. The moist precipitate was extracted with absolute ethanol (100 ml.) at 20°, the extract filtered, and anhydrous ether (150 ml.) added. The resulting solution was stored at −18° for 5 days. The precipitated needles were filtered off and washed with absolute ethanol (20 ml.), 1 : 1 ethanol–ether (20 ml.), and ether (50 ml.). The *compound* was dried *in vacuo* over anhydrous magnesium perchlorate, and was stored similarly (yield 0·9 g.) (Found: C, 43·2; H, 4·4. $C_4H_5ON_3$ requires C, 43·3; H, 4·5%). In the preparation, hydrochloric acid may be replaced by nitric acid. Carbamoylgloxaline sublimes above 200°. At room temperature it is insoluble in ethanol, chloroform, carbon tetrachloride, and carbon disulphide, and is sparingly soluble in water and in ethanol–water (95 : 5, v/v). It dissolves readily in hot water but probably decomposes in the process, since no precipitate is formed on subsequent cooling.

Enzymic formation of citrulline. Each tube contained 0·5M-maleic acid–potassium hydroxide buffer (0·1 ml.; pH 6·8), 0·1M-ornithine (0·2 ml.), sufficient water to make the final volume 1·0 ml., and, where indicated, an aqueous extract of an acetone powder of rat-liver mitochrondria (0·1 ml.; 0·8 mg. of protein), 0·5M-potassium phosphate buffer (0·2 ml.; pH 6·8), 0·05M-carbamoylglyoxaline (0·4 ml.) or 0·05M-potassium cyanate (0·4 ml.). The reaction was started by the addition of carbamoylglyoxaline or cyanate. The tubes were incubated at 38°

[1] Jones, Spector, and Lipmann, *J. Amer. Chem. Soc.*, 1955, **77**, 819; Hall, Marshall, and Cohen, *Biochim. Biophys. Acta*, 1955, **17**, 279.

for 15 min. and the reaction was stopped by the addition of ice-cold 0·5N-perchloric acid (5 ml.). The denatured protein was removed by centrifugation, and aliquot parts of the supernatant solution were analysed for citrulline[2]. Results are tabulated.

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BIOCHEMISTRY DEPARTMENT, UNIVERSITY OF OXFORD. [*Received, June 27th,* 1956.]

[2] Archibald, *J. Biol. Chem.*, 1944, **156**, 121.

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897. *Organic Peroxides. Part VII.* The Alkylation of Hydrogen Peroxide and Alkyl Hydroperoxides with Ethers.*

By ALWYN G. DAVIES and R. FELD.

ALKYL halides, sulphates, and sulphonates, alcohols, esters, and olefins have all been used for alkylating hydrogen peroxide and alkyl hydroperoxides to form alkyl hydroperoxides and dialkyl peroxides, respectively.[1] We now describe the analogous alkylation with ethers.

The mechanism of these reactions is undoubtedly similar to that which has been described for the analogous reaction of alcohols,[1] and involves nucleophilic attack of the peroxide molecule at a carbon atom, probably by an S_N1 or S_Ni mechanism.

Experimental.—In the following experiments precautions were taken against explosion.

Reactions of ethers with hydrogen peroxide. (i) *Ethyl 1-phenylethyl ether.* The ether (0·5 g.) was added at 0° with stirring to 90% hydrogen peroxide (8 c.c.) containing concentrated sulphuric acid (0·1 g.). The mixture was allowed to warm to room temperature and stirring was continued for a total of 6 hr. Water (25 c.c.) was then added and the organic layer was extracted with ether, washed with aqueous sodium hydrogen carbonate and with water, and dried (Na_2SO_4). Evaporation of the ether left an oil (0·1 g.) which was identified as 1-phenylethyl hydroperoxide by the preparation of its triphenylmethyl derivative,[2] m. p. 78—80°, mixed m. p. 79—81°. In the absence of sulphuric acid the ether was recovered after treatment with hydrogen peroxide for 1 hr.

(ii) *Ethyl triphenylmethyl ether.* A mixture of ethyl triphenylmethyl ether (0·6 g.) dissolved in the minimum of ether, and 90% hydrogen peroxide (4 c.c.) containing concentrated sulphuric acid (0·1 g.) likewise yielded triphenylmethyl hydroperoxide (0·48 g.), m. p. 86° (from light petroleum) (Found: C, 82·3; H, 5·8. Calc. for $C_{19}H_{16}O_2$: C, 82·6; H, 5·8%). Bisdiphenylmethyl ether was recovered after similar treatment. Bis-1-phenylethyl ether gave an oil, b. p. 165°/20 mm., which was mainly starting material but gave a strong peroxide test on starch–iodide paper.

(iii) *Bisdiphenylmethyl ether.* The ether (1·0 g.) was dissolved in a mixture of acetic acid (5 c.c.), 90% hydrogen peroxide (1 c.c.), and concentrated sulphuric acid (0·2 c.c.). After 4 hr. at room temperature the mixture yielded diphenylmethyl hydroperoxide (0·63 g.), m. p. 46·5—47° (from light petroleum) (Found: C, 77·6; H, 5·6. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·0%); triphenylmethyl derivative,[2] m. p. 84—86°; 9-xanthenyl derivative,[2] m. p. 115—117°.

Reactions of ethers with alkyl hydroperoxides. (i) *Ethyl triphenylmethyl ether.* Ethyl triphenylmethyl ether (0·37 g.), *tert.*-butyl hydroperoxide (0·12 g.), acetic acid (3 c.c.), and concentrated sulphuric acid (0·05 c.c.) were mixed. After 6 hr. at room temperature the mixture was poured into water, yielding *tert.*-butyl triphenylmethyl peroxide[2] (0·24 g.), m. p. and mixed m. p. 69—71°.

(ii) iso*Propyl triphenylmethyl ether.* The ether (0·54 g.), acetic acid (5 c.c.), concentrated sulphuric acid (0·05 c.c.), and $\alpha\alpha$-dimethylbenzyl hydroperoxide (0·29 g.) were mixed. After 3 hr. the mixture was diluted with water, yielding a solid (0·44 g.) which was insoluble in the common organic solvents. It was purified by washing it with a large volume of hot ethanol, giving $\alpha\alpha$-dimethylbenzyl triphenylmethyl peroxide,[2] m. p. and mixed m. p. 169—170°.

(iii) *Bisdiphenylmethyl ether.* The ether (2·0 g.) and *tert.*-butyl hydroperoxide (1·04 g.) were dissolved in acetic acid (20 c.c.) containing concentrated sulphuric acid (0·8 g.). After 6 hr.

* Part VI, *J.*, 1956, 665.

[1] References are given in Part VI, Davies and Feld, *J.*, 1956, 665.

[2] Davies, Foster, and White, *J.*, 1954, 2200.

the mixture was poured into water yielding tert.-*butyl diphenylmethyl peroxide* (1·46 g.), b. p. 85° (bath)/0·001 mm., n_D^{25} 1·5463 (Found: C, 79·5; H, 7·2. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·85%).

We are indebted to Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., for their interest and encouragement, to Laporte Chemicals Limited for the gift of concentrated hydrogen peroxide, and to the Governing Body of Battersea Polytechnic for the award of an Edwin Tate and Holl Scholarship (to R. F.).

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[*Received, July 19th,* 1956.]

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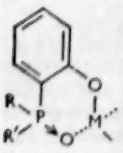
898. *Organic Complex-forming Agents for Metals. Part III.* Compounds containing the o-Hydroxyphenylphosphine Oxide Group.*

By J. KENNEDY, E. S. LANE, and J. L. WILLANS.

THERE is some evidence to suggest that the phosphine oxide group can form complexes with certain metals, *e.g.*, uranium,[1] by donation of two electrons from the oxygen atom. If this is so, a compound containing the *o*-hydroxyphenylphosphine oxide group should chelate with metals, as in (I), as "oxine" does. Since it represents a completely new chelating system some compounds containing such ligands were prepared and examined.



(I)

Di-(*o*-methoxyphenyl)methylphosphine was obtained in 70% yield by treatment of methylphosphonous dichloride with *o*-methoxyphenylmagnesium bromide, and was characterised as the sulphide and as a phosphonium salt; it oxidised to the phosphine oxide with hydrogen peroxide. It was also prepared (84% yield) by alkaline hydrolysis of tri-(*o*-methoxyphenyl)methylphosphonium iodide, itself prepared by quaternisation of tri-(*o*-methoxyphenyl)phosphine with methyl iodide. Di-(*o*-hydroxyphenyl)methylphosphine oxide was obtained on dealkylation of the dimethoxy-oxide with aluminium chloride or pyridine hydrochloride and was characterised as the diacetate.

Tri-(*o*-hydroxyphenyl)phosphine oxide was similarly obtained (79% yield), with aluminium chloride, and was characterised as the triacetate.

In contradistinction to the methoxy-derivatives, both compounds containing the *o*-hydroxyphenylphosphine oxide group gave precipitates with solutions containing Fe^{3+}, UO_2^{2+}, and Hg^{2+}, but apart from establishing this grouping as a chelating system this ligand is unlikely to be of analytical interest because of its low sensitivity and lack of selectivity.

We were unable to prepare the related *o*-hydroxyphenylphosphonic acid, the phosphorus analogue of salicylic acid. Attempts to demethylate *o*-methoxyphenylphosphonic acid caused breakage of the C–P bond, and *o*-benzyloxyaniline (which we hoped to debenzylate later by hydrogenation) did not undergo the Freeman–Doak reaction for replacement of the amino-group by phosphonic acid.

Experimental.—Determination of phosphorus in aromatic phosphines, phosphine oxides, and phosphonium salts. Wet oxidation methods were ineffective for the digestion of these classes of compounds to orthophosphate. Fusion with sodium peroxide (cf. Stanley *et al.*[2]) was satisfactory.

Determination of the equivalent weight of organo-phosphorus compounds. Phosphines and phosphonium salts were titrated with perchloric acid in acetic acid (see Parts I and II). Phosphine oxides were insufficiently basic for this technique. *o*-Hydroxyphenylphosphine oxides were titrated as phenols in ethylenediamine.

Tri-(o-methoxyphenyl)methylphosphonium iodide, prepared quantitatively from methyl iodide

* Part II, *J.*, 1956, 569.

[1] Blake, Brown, and Coleman, ORNL 1946 (Chemistry), 1955.
[2] Stanley, Vannier, Freeman, and Doak, *Analyt. Chem.*, 1955, **27**, 474.

and the parent tertiary phosphine,[3] had m. p. 212—213° (Found: C, 53·0; H, 4·7; I, 26·1. $C_{22}H_{24}O_3IP$ requires C, 53·4; H, 4·9; I, 25·7%).

Tri-(o-hydroxyphenyl)phosphine oxide. To tri-(*o*-methoxyphosphine) oxide[4] (50 g.) and anhydrous aluminium chloride (72·5 g.), benzene (150 ml.) was added with stirring. Methyl chloride was evolved. The mixture was kept at 95—100° for 4 hr., evolution of methyl chloride then ceasing. After acidification with 20% hydrochloric acid (250 ml.) the benzene was removed in steam, leaving a solid. This was filtered off and recrystallisation (alcohol) gave a colourless *iodide* (35 g.), m. p. 214·5—216° (Found: C, 66·2; H, 4·8; P, 9·1%; equiv., 107. $C_{18}H_{15}O_4P$ requires C, 66·25; H, 4·6; P, 9·5%; equiv., 109). The *triacetate* had m. p. 197—199° (Found: C, 64·5; H, 5·0; P, 6·7. $C_{24}H_{21}O_7P$ requires C, 63·7; H, 4·6; P, 6·9%).

Di-(o-methoxyphenyl)methylphosphine. Methylphosphonous dichloride (13·1 g.) in dry ether (50 ml.) was added dropwise to a cooled, stirred solution of *o*-methoxyphenylmagnesium bromide (from 47 g. of *o*-bromoanisole) in ether (150 ml.). After 1 hr. the mixture was decomposed by saturated aqueous ammonium chloride, and the ether layer was evaporated. The residue recrystallised from alcohol, giving the *phosphine* (20·1 g.), m. p. 128—129° (Found: C, 69·4; H, 6·6; P, 11·5%; equiv., 262. $C_{15}H_{17}O_2P$ requires C, 69·3; H, 6·5; P, 11·9%; equiv., 260). With methyl and ethyl iodide respectively it gave quantitative yields of the corresponding *phosphonium iodides*, m. p. 215—216·5° (Found: equiv., 402. $C_{16}H_{20}O_2IP$ requires equiv., 402), and m. p. 157—160° (Found: C, 48·9; H, 4·9; P, 7·45%; equiv., 418. $C_{17}H_{23}O_2IP$ requires C, 49·0; H, 5·3; P, 7·45%; equiv., 416).

Di-(o-methoxyphenyl)methylphosphine oxide. (*a*) The preceding phosphine (14·1 g.) in water (20 ml.) at 60° was treated with hydrogen peroxide (15 ml.; 100-vol.) dropwise. The mixture was refluxed for 10 min., then cooled; the lower oily layer solidified and recrystallised from alcohol, giving a quantitative yield of the *oxide*, m. p. 150° (Found: C, 64·9; H, 6·25; P, 11·2. $C_{15}H_{17}O_3P$ requires C, 65·2; H, 6·2; P, 11·2%).

(*b*) Tri-(*o*-methoxyphenyl)methylphosphonium iodide (9·88 g.) was refluxed for 2 hr. with 20% aqueous potassium hydroxide (40 ml.), then steam-distilled to remove anisole, and the residue was filtered off and recrystallised from benzene, giving the oxide, m. p. 150—151·5° (Found: C, 65·4; H, 6·5%).

The corresponding *phosphine sulphide*, obtained by the exothermic reaction between sulphur and the parent phosphine in ether, had m. p. 87—88° (from ethanol) (Found: P, 15·1; S, 16·0. $C_9H_{13}OSP$ requires P, 15·5; S, 16·0%).

Di-(o-hydroxyphenyl)methylphosphine oxide. (*a*) Di-(*o*-methoxyphenyl)methylphosphine oxide (13·8 g.) was refluxed for 1 hr. with benzene and aluminium chloride (70·0 g.). Evaporation of the benzene layer, followed by recrystallisation from alcohol, gave the *phenol* (5·8 g.), m. p. 204·5—206° (Found: P, 12·5. $C_{13}H_{13}O_3P$ requires P, 12·5%). The *diacetate* had m. p. 201—203° (Found: C, 61·6; H, 5·25; P, 9·15%; equiv., 164. $C_{17}H_{17}O_5P$ requires C, 61·5; H, 5·1; P, 9·35%; equiv., 168).

(*b*) Di-(*o*-methoxyphenyl)methylphosphine oxide (6·5 g.) and pyridine hydrochloride (15 g.) were heated together at 200° for 4 hr., then poured into water. The phenol separated (3·0 g.). The m. p. was raised to 210·5—211·5° by alternate dissolution in alkali and precipitation with acid (Found: P, 12·5%).

Sensitivity and selectivity tests. The method of Irving *et al.*[5] was used. The results are expressed as volumes of standard metal solutions which (*a*) gave a perceptible precipitate (V_1) and (*b*) failed to give a precipitate (V_2). The larger volume V_1 was taken as a conservative estimate of the sensitivity. The results are expressed in terms of p*L* [$-\log_{10}$ (limiting concentration in g.-equivs. per l.)] for the volumes V_1 and V_2 respectively. The following ions were tested: Cu^{2+}, Fe^{3+}, UO_2^{2+}, Mg^{2+}, Hg^{2+}, Ni^{2+}, and Co^{2+}.

Tri(*o*-hydroxyphenyl)phosphine oxide at pH 5·3: Fe^{3+}, 4·24—4·54; UO_2^{2+}, 3·24—3·54; Hg^{2+}, 2·24—3·24.

Di-(*o*-hydroxyphenyl)methylphosphine oxide at pH 5·3: Fe^{3+} 3·24—4·24; UO_2^{2+} 2·24—2·73; Hg^{2+} 2·24—2·84; and at pH 8·5: Fe^{3+}, 3·24—4·24; UO_2^{2+}, 3·24—4·24.

The colours of the precipitates obtained with both compounds and Fe^{3+}, UO_2^{2+}, and Hg^{2+} were red-brown, pale brown, and white respectively.

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[*Received, May 28th, 1956.*]

[3] Mann and Chaplin, *J.*, 1937, 527.
[4] Dawson and Burger, *J. Org. Chem.*, 1953, **18**, 207.
[5] Irving, Butler, and Ring, *J.*, 1949, 1489; cf. Hollingshead, *Chem. and Ind.*, 1944, 440; Irving, Hollingshead, and Harris, *Analyst*, 1955, **80**, 260; Hollingshead, *Analyt. Chim. Acta*, 1955, **12**, 201.

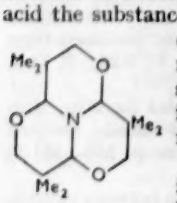
899. *The Reaction of Ammonium Acetate with β-Hydroxy-αα-dimethylpropaldehyde.*

By J. F. Cavalla.

Some two years ago [1] a by-product $C_{15}H_{27}O_3N$ was obtained during preparation of 2-cyano-5-hydroxy-4 : 4-dimethylpent-2-enolactone from β-hydroxy-αα-dimethylpropaldehyde, ammonium acetate, and acetic acid in benzene (cf. Cope [2]). Further work has shown that the nitrogen atom in the by-product came from the ammonium acetate rather than from the ethyl cyanoacetate. Acetic acid in stoicheiometric amounts had also to be present to give good yields.

The compound was remarkably stable to all except drastic conditions. It was recovered unchanged from boiling dilute hydrochloric acid or 5% ethanolic sodium hydroxide (3 hr.); acetic anhydride at the b. p. or in pyridine at 95°, and methyl iodide alone or in boiling nitromethane or acetonitrile had no effect, the compound crystallising well from the anhydride or iodide.

The absence of carbonyl groups, indicated by the compound's inertness to the common reagents, was confirmed by the lack of both ultraviolet and infrared absorption. When refluxed with constant-boiling hydrochloric acid or phosphorus in phosphoric–hydriodic acid the substance decomposed to give formaldehyde, *iso*butyraldehyde, and β-hydroxy-αα-dimethylpropaldehyde, identified by paper chromatography. The molecular formula, preparation, and properties indicate a probable structure (I) and this view is shared by Lynn [3] who has isolated what is almost certainly the same compound by treating β-hydroxy-αα-dimethylpropaldehyde with ammonia.



(I)

However, whilst the compound can be titrated with perchloric acid in acetic acid its pK_a is remarkably low (<2); it yields a perchlorate but not a hydrochloride. Unlike the oxazolidines,[4] which resemble the postulated formula, the compound resisted hydrogenation even under forcing conditions (5% palladised charcoal in ethanol at 100°/80 atm.). It also did not react with ethereal methylmagnesium iodide which is known to react with the grouping $NR_2{\cdot}C(OR)<$.[4,5]

Experimental.—Reaction of β-hydroxy-αα-dimethylpropaldehyde with ammonium acetate and acetic acid. The aldehyde (30·6 g., 0·3 mol.), ammonium acetate (15·4 g., 0·2 mol.), and acetic acid (12 g., 0·2 mol.) in benzene (100 ml.) were refluxed under a Dean and Stark head. After 3 hr., 9 ml. of water had collected and refluxing was stopped. On cooling, needles separated (15·6 g., m. p. 183—186°). The mother-liquor on dilution with light petroleum (200 ml.) gave a less pure product (3·5 g; m. p. 165—180°). One crystallisation from chloroform–ethanol gave *dodecahydro-3 : 3 : 6 : 6 : 9 : 9-hexamethyl-1 : 4 : 7-trioxa-9b-azaphenalene* (I), m. p. 185—187° (71%) (Found: C, 66·9; H, 10·4; N, 5·2; O, 17·7%; *M*, 256. $C_{15}H_{27}O_3N$ requires C, 66·9; H, 10·1; N, 5·2; O, 17·8%; *M* 269), which had no significant absorption above 215 mμ and gave infrared max. at 2950, 2850, 2800, 2700, 2590, 1478, 1461, 1396, 1374, 1365, 1317, 1300, 1246, 1222, 1204, 1138, 1087, 1048, 1020, 998, 965, 952, 938, 926, 907, 808, and 698 cm.$^{-1}$ in a potassium bromide disc.

If the acetic acid was omitted from the above reaction mixture no product was obtained; addition of small quantities (0·2 g.) of acid gave only 0·4 g. of product.

Reactions. The substance (0·4 g.) in ether (50 ml.) was treated with a dilute solution of perchloric acid in ether (50 ml.); the *perchlorate* separated as needles (0·4 g.), m. p. 248° (decomp.). Crystallisation from ethanol–ether gave prisms, m. p. 250° (decomp.) (Found: C, 49·1; H, 7·6; N, 3·7. $C_{15}H_{27}O_3N,HClO_4$ requires C, 48·7; H, 7·6; N, 3·8%).

The substance (1·5 g.) was refluxed for 1 hr. with constant-boiling hydrochloric acid (150 ml.),

[1] Bowman and Cavalla, *J.*, 1954, 1171.
[2] Cope, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.
[3] Lynn, *ibid.*, 1955, **77**, 6067.
[4] Senkus, *ibid.*, 1945, **67**, 1515.
[5] Robinson and Robinson, *J.*, 1923, 532.

then distilled, the first 10 ml. of distillate being collected. Treatment with Brady's solution gave an immediate precipitate, m. p. 145—160°. This was run upwards on chromatography paper with the top layer of a light petroleum (b. p. 100—120°)–methanol mixture : three spots were obtained, having R_F 0·15, 0·26, and 0·58 and shown to be those for the 2 : 4-dinitrophenylhydrazones of β-hydroxy-αα-dimethylpropaldehyde, formaldehyde, and *iso*butyraldehyde respectively. Basification or dilution of the acid solution remaining from the distillation gave some unchanged starting material.

The compound did not react with lithium aluminium hydride in boiling ether during 4 hr.

The author thanks Mr. A. J. Durre of this laboratory and Frau E. Pascher (Bonn) for the microanalyses and Miss E. Tanner for the physical measurements, also Dr. R. E. Bowman for many helpful discussions.

PARKE, DAVIS & COMPANY LIMITED,
STAINES ROAD, HOUNSLOW, MIDDLESEX. [*Received, June 21st,* 1956.]

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900. 2 : 6-*Dimethylacetophenone.*

By (the late) E. A. BRAUDE and R. L. ERSKINE.

2 : 6-DIMETHYLACETOPHENONE (I) has been prepared by several methods, *inter alia* from 2 : 6-dimethylbenzonitrile,[1] 2 : 6-dimethylbenzoic acid,[2,3] and 2-iodo-1 : 3-dimethylbenzene,[4] but some of the physical properties recorded for it by different workers are not in good agreement. Since the ketone is liquid and does not readily furnish crystalline derivatives, the discrepancies could conceivably be due to the presence of isomers. The spectral properties are of importance in connection with the theory of steric hindrance in conjugated systems [3] and we have therefore re-investigated this compound.

2 : 6-Dimethylacetophenone was prepared from the nitrile by reaction with methylmagnesium iodide in anisole, followed by acid hydrolysis. The ketone, which is somewhat unstable in air, shows ultraviolet absorption with an inflexion at about 2400 Å (ε 2000) in ethanol, and infrared absorption with intense peaks at 1700 (CO stretching) and 773 cm.$^{-1}$ (1 : 2 : 3-trisubstituted benzene). When heated with Brady's reagent, it furnished a 2 : 4-dinitrophenylhydrazone, m. p. 158°, identical with that previously described,[1,3] but the yield was only 30% under the best conditions tried. The structure and homogeneity of the ketone was confirmed by conversion [4] with potassium hypochlorite into 1 : 3-dimethyl-2-trichloroacetylbenzene (II), followed by alkaline hydrolysis in a *glass* vessel to 2 : 6-dimethylbenzoic acid (III).

When the hydrolysis of the trichloro-ketone was conducted in a copper flask, the acid (III) was obtained in lower yield, together with a second acid $C_{10}H_{12}O_3$, m. p. 152°. This must be 2 : 6-dimethylmandelic acid (IV), since the infrared spectrum indicates the presence of a hydroxyl group and a non-conjugated carboxyl group, and the acid is converted by chromic oxide into 2 : 6-dimethylbenzaldehyde (VI), presumably *via* 2 : 6-dimethylglyoxylic acid (V) followed by decarboxylation. 2 : 6-Dimethylmandelic acid has been reported by Ando [5] to have m. p. 115°, but his product, obtained by the reaction between *m*-xylene and oxomalonic ester, was actually 2 : 4-dimethylmandelic acid.[6] The formation of the mandelic acid (IV) from the ketone (II) can be rationalized either by a copper-catalysed reduction of the carbonyl group at some stage in the hydrolysis or by an initial hydrogenolysis of one C–Cl bond followed by hydrolysis and rearrangement [7] of the resulting 2 : 6-dimethylphenylglyoxal.

These results, which have been duplicated several times, suggest that some of the samples of 2 : 6-dimethylacetophenone previously used for spectral measurements were impure.

[1] Pearson and Greer, *J. Amer. Chem. Soc.*, 1955, **77**, 1294; cf. Charlton and Hughes, *J.*, 1954, 2939.
[2] De Jong, *Rec. Trav. chim.*, 1942, **61**, 539.
[3] Braude and Sondheimer, *J.*, 1955, 3754.
[4] Schwartzman and Corson, *J. Amer. Chem. Soc.*, 1954, **76**, 781.
[5] Toshio Ando, *J. Chem. Soc. Japan*, 1935, **56**, 745.
[6] Riebsomer, Irvine, and Andrews, *J. Amer. Chem. Soc.*, 1938, **60**, 1015.
[7] Evans, *Amer. Chem. J.*, 1906, **35**, 115.

The present results correspond closely to those reported by Schwartzman and Corson,[4] except that their material showed a peak at 1658 cm.$^{-1}$, possibly due to 2 : 6-dimethylstyrene. It is surprising that Schwartzman and Corson's ketone did not furnish [4] the 2 : 4-dinitrophenylhydrazone, m. p. 158°, but afforded [3] instead an unidentified derivative,

$$\underset{\text{(I)}}{R\cdot CO\cdot CH_3} \longrightarrow \underset{\text{(II)}}{R\cdot CO\cdot CCl_3} \longrightarrow \underset{\text{(III)}}{R\cdot CO_2H} \qquad \underset{\text{(IV)}}{R\cdot CH(OH)\cdot CO_2H} \longrightarrow \underset{\text{(V)}}{R\cdot CO\cdot CO_2H} \longrightarrow \underset{\text{(VI)}}{R\cdot CHO}$$

(R = 2 : 6-$C_6H_3Me_2$)

m. p. 223°; it is difficult to account for this except by prior decomposition of the ketone. We have been unable to repeat the preparation [3] of 2 : 6-dimethylacetophenone by the action of methyl-lithium on 2 : 6-dimethylbenzoic acid, mostly unchanged acid being recovered in each attempt; although the ketone previously obtained gave a 2 : 4-dinitrophenylhydrazone, m. p. 155°, the ultraviolet light absorption of the product, $\lambda_{max.}$ 2510 Å (ε 5600) is not that of 2 : 6-dimethylacetophenone.

The present results necessitate some revision of the earlier discussion.[3] The ultraviolet light absorption of 2 : 6-dimethylacetophenone is very similar to that of 2 : 4 : 6-trimethylacetophenone; application of the equation $\cos^2\theta = \varepsilon/\varepsilon_0$ to the reduction in intensity of the characteristic band relative to acetophenone leads to values of 70° and 63°, respectively, for the interplanar angle θ between the phenyl and the carbonyl chromophore, showing that the steric effects of the two *o*-methyl substituents are comparable in the two compounds. The influence of the *p*-methyl substituent is to reduce θ slightly; the same effect is observed in comparing 2-methyl- and 2 : 4-dimethyl-acetophenone and may be ascribed to the hyperconjugative increase in the bond order of the bond between the substituted phenyl and the carbonyl group which will promote the planarity of the conjugated system. It may be noted that the decreases in intensity are accompanied by small, but by no means negligible, displacements to shorter wavelengths; if it is assumed that, in the absence of steric effects, *o*-methyl groups would produce bathochromic shifts similar to those observed with *p*-methyl groups ($\Delta\lambda = 90$ Å), the $\Delta\lambda$ values due to steric effects are *ca.* −210 Å for 2 : 6-dimethyl- and −280 Å for 2 : 4 : 6-trimethyl-acetophenone, corresponding to increases of *ca.* 12—14 kcal. in transition energy compared with that of acetophenone. Acetophenones carrying two *o*-methyl substituents thus represent border-line cases between what have been termed steric effects of type (1) and type (2).

Experimental.—*2 : 6-Dimethylacetophenone.* 2 : 6-Dimethylbenzonitrile (8·7 g.; m. p. 90—91°, $\lambda_{max.}$ 2310 Å, ε 10,000 in EtOH) in dry anisole (120 ml.) was added to methylmagnesium iodide (1·1 mol.) in ether (100 ml.). The ether was distilled off and the residual solution was refluxed for 3 hr. Excess of saturated aqueous ammonium chloride was then added, the mixture was extracted with ether, the ether solution was extracted with N-sulphuric acid (3 × 50 ml.), and the acid solution was refluxed with toluene (50 ml.) for 12 hr. The toluene layer was separated, the aqueous layer was extracted with ether, and the combined toluene–ether solutions were washed with 2N-sodium carbonate solution and water, dried (Na_2SO_4), and distilled, to give 2 : 6-dimethylacetophenone (5·2 g., 44%) as a colourless oil, b. p. 106°/17 mm., n_D^{27} 1·5141 (Found: C, 81·0; H, 8·3. Calc. for $C_{10}H_{12}O$: C, 81·0; H, 8·1%). Infrared spectrum (liquid film): $\nu_{max.}$ 1700 s, 1592 m, 1461 m, 1420 m, 1381 w, 1350 s, 1254 s, 1165 w, 1106 w, 1054 m, 959 m, 773 s, and 744 m cm.$^{-1}$.

The ketone (0·3 g.) was heated under reflux with 2 : 4-dinitrophenylhydrazine (0·5 g.), ethanol (10 ml.), and sulphuric acid (1 ml.). The 2 : 4-dinitrophenylhydrazone (0·23 g., 30%) crystallised from methyl*cyclo*hexane as yellow needles, m. p. 158°, $\lambda_{max.}$ 3640 Å (ε 23,000) in $CHCl_3$ (Found: C, 59·0; H, 5·1; N, 16·8. Calc. for $C_{16}H_{16}O_4N_4$: C, 58·5; H, 4·9; N, 17·1%). When hydrochloric acid was used [4] in place of sulphuric acid, the yield of derivative was slightly lower.

Oxidation. The ketone was converted by potassium hypochlorite at 55° (3 hr.) into the 1 : 3-dimethyl-2-trichloroacetylbenzene (75%), b. p. 139°/11 mm., n_D^{22} 1·5412. Hydrolysis by refluxing 2N-sodium hydroxide (6 hr.) in a glass vessel gave 2 : 6-dimethylbenzoic acid (85%), m. p. 115°. Hydrolysis in a copper flask under otherwise identical conditions gave 2 : 6-dimethylbenzoic acid (56%) and 2 : 6-dimethylmandelic acid (33%) which were separated

by partition between benzene and water. After sublimation at 140°/15 mm., the very water-soluble 2 : 6-*dimethylmandelic acid* crystallised from benzene in needles, m. p. 152° (Found : C, 66·5; H, 6·8. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%). Infrared spectrum (in paraffin mull) : $\nu_{max.}$ 3400 m (OH), 1709 s (CO_2H), and 1590 w, 1168 m, 1078 m, 891 w, and 777 s cm.$^{-1}$ (1 : 2 : 3-trisubstituted benzene ring).

A stirred mixture of 2 : 6-dimethylmandelic acid (0·21 g.), pyridine (5 ml.), and chromic oxide (0·28 g.) was kept for 12 hr. at 20°. Water (20 ml.) was added and the mixture was continuously extracted with ether. The ether extract was concentrated and treated with Brady's reagent, giving the 2 : 4-dinitrophenylhydrazone of 2 : 6-dimethylbenzaldehyde (0·13 g.) as red prisms, m. p. and mixed m. p. 255°, $\lambda_{max.}$ 3780 Å (ε 26,500) in $CHCl_3$ (Found : C, 57·7; H, 4·7; N, 17·7. Calc. for $C_{15}H_{14}O_4N_4$: C, 57·3; H, 4·5; N, 17·8%). The infrared spectrum (KBr disc) was indistinguishable from that of an authentic sample and showed bands with $\nu_{max.}$ 3240 w, 1615 s, 1590 s, 1505 s, 1327 s, 1255 m, 1215 m, 1127 s, 836 m, 788 m, 780 m, 739 m cm.$^{-1}$.

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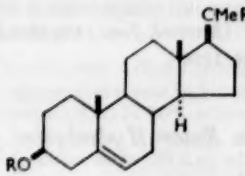
901. 20ξ-*Hydroxycholesterol.*

By Vladimir Petrow and (Mrs.) Isobel A. Stuart-Webb.

Presumptive evidence exists [1] that 20-hydroxycholesterol (Ia) is an intermediate in corticosteroid biogenesis. We have, therefore, prepared a 20ξ-hydroxycholesterol (Ib) and some simpler analogues for biological study.

A previous attempt [2] to prepare the compound (Ib) by reacting *iso*hexylmagnesium bromide with 3β-acetoxypregn-5-en-20-one (Ic) gave "unsatisfactory results." In our hands, however, smooth condensation occurred to give, after acetylation, 3β-acetoxy-20ξ-hydroxycholesterol (Id) in *ca.* 45% yield. The constitution assigned to this product was supported by its infrared absorption spectrum, for which we are indebted to Mr. R. F. Branch, B.Sc. (Ministry of Supply), which showed the presence of a non-hydrogen-bonded hydroxyl group in the molecule. Alkaline hydrolysis at room temperature yielded 20ξ-hydroxycholesterol (Ib), which was converted by the Oppenauer route into 20ξ-hydroxycholest-4-en-3-one.



(Ia): R = H, R' = —OH, R'' = ···$[CH_2]_3$·$CHMe_2$

(Ib): R = H, R' = ~~OH, R'' = ~~$[CH_2]_3$·$CHMe_2$

(Ic): R = Ac, R'R'' = O

(Id): R = Ac, R' = ~~OH, R'' = ~~$[CH_2]_3$·$CHMe_2$

Some simpler analogues of (Ib), prepared in similar manner, are listed in the Table.

In no case was there any evidence for the formation of more than one $C_{(20)}$-stereoisomer. The stereochemistry of the products remains unestablished. Discussion of this point with Dr. W. Klyne, however, leads us to believe that the compounds have probably the same configuration at $C_{(20)}$ as has cholesterol.[4]

Experimental.—Optical rotations were measured in chloroform in a 1-dm. tube. The ultraviolet absorption spectrum was kindly determined by Mr. M. T. Davies, B.Sc.

4-Methylpentan-1-ol was prepared essentially as described by Cardwell *et al.*[3] It was converted into *iso*hexyl bromide by Sabetay and Bléger's method.[3]

3β-*Acetoxycholest-5-en*-20ξ-*ol* (Id). 3β-Acetoxypregn-5-en-20-one (3·58 g.) in benzene (150

[1] Cf. for example, Lynn, jun., Staple, and Gurin, *Fed. Proc.*, 1955, **14**, 783.
[2] Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, 361.
[3] Sabetay and Bléger, *Bull. Soc. chim. France*, 1930, **47**, 885.
[4] Cf. Klyne, "Ciba Foundation Colloquia on Endocrinology," Vol. VII, p. 150.

ml.) was added to the Grignard solution prepared from magnesium (2·4 g.), *iso*hexyl bromide (1·65 g.), and ether (100 ml.). The mixture was distilled until the distillate temperature reached 78° and gently refluxed thereafter for a further 3 hr. After cooling, the mixture was decomposed with ammonium chloride solution, and the product isolated with benzene. The resulting oil was acetylated (acetic anhydride–pyridine for 1 hr. on the water-bath), and a benzene solution of the product was chromatographed on alumina (100 g.; B.D.H. chromatography grade). The benzene–ether (6·5 : 1) eluates yielded 3β-*acetoxycholest-5-en-20ξ-ol*, needles (from methanol), m. p. 155—156°, $[\alpha]_D^{23}$ −58° (*c*, 0·455) (Found: C, 78·8; H, 11·0. $C_{29}H_{48}O_3$ requires C, 78·4; H, 10·8%).

Cholest-5-ene-3β : 20ξ-diol (Ib). The acetate (220 mg.) in methanol (20 ml.) was treated with potassium carbonate (140 mg.) in water (2 ml.) overnight at room temperature. The product was isolated with chloroform and crystallised from acetone–hexane, giving *cholest-5-ene-3β : 20ξ-diol*, m. p. 123—125°, $[\alpha]_D^{22}$ −52° (*c*, 0·369) (Found: C, 80·4; H, 11·5. $C_{27}H_{46}O_2$ requires C, 80·6; H, 11·4%).

20ξ-Hydroxycholest-4-en-3-one. 20ξ-Hydroxycholesterol (1 g.) in *cyclo*hexanone (13 ml.) was oxidised with aluminium *tert.*-butoxide (1 g.) in toluene (8 ml.) under reflux for 40 min. Crystallisation from aqueous methanol furnished *20ξ-hydroxycholest-4-en-3-one*, needles, m. p. 137—138°, $[\alpha]_D^{22}$ +66° (*c*, 0·592), $\lambda_{max.}$ 241 mμ (log ε 4·23) (Found: C, 80·5; H, 11·0. $C_{27}H_{44}O_2$ requires C, 81·0; H, 11·0%).

Condensation of 3β-acetoxypregn-5-en-20-one with alkyl halides followed the general pattern employed for the preparation of compound (Ic). The products obtained are listed in the Table (the hydroxyl group and the 20-substituent are of unknown orientation).

(I; R′ = OH)					Analysis				
					Found, %			Reqd., %	
R	R″	M. p.	$[\alpha]_D^t$	*c*	C	H	Formula	C	H
H	Me	187°	−65° [a]	0·291	79·3	10·4	$C_{22}H_{36}O_3$	79·5	10·8 [d]
H	Et	167—168	−65 [b]	0·46	77·5	10·8	$C_{23}H_{38}O_3,\frac{1}{2}H_2O$	77·8	11·0
Ac	Et	172—173	−64 [c]	0·823	77·5	10·6	$C_{25}H_{40}O_3$	77·3	10·3
H	*n*-Bu	112—114	—	—	76·0	11·1	$C_{25}H_{42}O_3,H_2O$	76·5	11·2
H	*n*-C_5H_{11}	123	−61 [b]	0·604	80·7	11·2	$C_{26}H_{44}O_3$	80·4	11·3
Ac	*n*-C_5H_{11}	155	−57 [c]	0·402	77·8	10·6	$C_{28}H_{46}O_3$	78·1	10·7

[a] t = 23°. [b] t = 24°. [c] t = 22°. [d] Cf. ref. 5.

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

Chemical Research Laboratories,
The British Drug Houses Ltd., London, N.1. [*Received, June 14th*, 1956.]

[5] Marker, Crooks, Jones, and Shabica, *J. Amer. Chem. Soc.*, 1942, **64**, 1276.

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902. *The Kinetics of Alkyl–Oxygen Fission in Ester Hydrolysis. Part VI.* Olefin Formation.*

By J. G. Hawke and V. R. Stimson.

Bunton [1] has shown that *iso*butene is formed in the acid-catalysed methanolysis of *tert.*-butyl benzoate. The present results (Tables 1 and 2) show that olefin is produced according to first-order kinetics during hydrolyses of *tert.*-butyl benzoate and 2 : 4 : 6-trimethylbenzoate, and *tert.*-amyl benzoate for which mechanism $A_{AL}1$ has been proposed.[2] The ratios of olefin-producing reaction to total reactions are independent of the nature of R′ in R′·CO_2R and, with allowance for the change in temperature, are closely comparable with the values found by Hughes *et al.*[3] for the *tert.*-butyl and *tert.*-amyl halides. Such results for olefin production indicate the formation of the carbonium ion R^+ and are further evidence for the unimolecular nature of these hydrolyses.

* Part V, *J.*, 1956, 3629.

[1] See Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 780.
[2] Stimson, *Nature*, 1955, **175**, 47; Parts I and III, *J.*, 1954, 2848; 1955, 2673.
[3] Hughes and MacNulty, *J.*, 1937, 1283; Cooper, Hughes, and Ingold, *J.*, 1937, 1280.

Rate of Hydrolysis and Acidity Function.—On a number of occasions [4] it has been shown that for a unimolecular acid-catalysed reaction the rate is proportional to the Hammett acidity function H_0, whereas for a bimolecular reaction involving a molecule of water the

TABLE 1. *Olefin produced from* tert.*-butyl 2 : 4 : 6-trimethylbenzoate.* C_A *and* C_E *are the concentrations of hydrochloric acid and ester respectively.*

Solvent: 80% ethanol. $C_A = 1{\cdot}03$; $C_E = 0{\cdot}086$; $Na_2S_2O_3 = 0{\cdot}01970$N; ester $= 4{\cdot}29 \times 10^{-3}$ mole; $\tau = 24$ and 48 hr.

Time (t, hr.)	3	6	9	12	15	24	27	30	33
Titre (T, c.c.)	9·13	17·34	24·43	29·52	34·03	42·97	45·00	47·22	48·71
$\log_{10}(T_{t+\tau} - T_t)$ ...	—	—	—	—	—	1·633	1·555	1·475	1·385
Time (t, hr.)	36	39	48	51	54	57	60	63	
Titre (T, c.c.)	50·05	51·04	54·44	55·05	55·65	56·31	56·88	57·42	
$\log_{10}(T_{t+\tau} - T_t)$ ...	1·312	1·231	1·736	1·662	1·583	1·503	1·437	1·369	

TABLE 2. *Olefin production in* 80% *ethanol at* 49°.

$C_A = 1{\cdot}03$.

	Ester (10^{-3}mole)	$10C_E$	10^3k_1 (hr.$^{-1}$)	$10^3k_1/C_A$ (hr.$^{-1}$ l. mole^{-1})	Olefin (10^{-3}mole)	Olefin (proportion)
Bu^t benzoate	5·55	1·11	6·4	6·2	0·75	0·13
Bu^t 2 : 4 : 6-trimethyl-benzoate	4·29	0·86	6·0	5·8	0·57	0·13
tert.-Amyl benzoate	4·92	0·97	8·4	8·2	1·88	0·38
	5·06	1·00	8·2	8·0	2·06	0·40

TABLE 3. *First-order rate constants for acid-catalysed hydrolyses.*

Temp. 50·0°. Solvent: 80% ethanol. $C_E = 0{\cdot}28$ mole/l.

C_A (mole/l.)	0·1	1·0	Factor
Bu^t benzoate (min.$^{-1}$)	$7{\cdot}5 \times 10^{-6}$	$1{\cdot}45 \times 10^{-3}$	19
Bu^t 2 : 4 : 6-trimethylbenzoate (min.$^{-1}$)	$5{\cdot}5 \times 10^{-6}$	$1{\cdot}27 \times 10^{-3}$	23

rate is proportional to the stoicheiometric concentration of hydrogen ion.[5] Acidity function (H_0) measurements in 80% ethanol are available for 0·1 and 1M-hydrochloric acid [6] and indicate a ratio in rate of 20·4 between these concentrations if H_0 be followed, whereas the factor would be 10 if the rate were proportional to the stoicheiometric concentration. The former is more nearly the case (Table 3), which substantiates the proposal of a unimolecular mechanism.

Experimental.—Olefin estimation. Nitrogen (20 c.c./min.), saturated with 80% ethanol at room temperature, was bubbled through a solution of the ester (*ca.* 1 g.) and hydrogen chloride (N concentration) in 80% ethanol (50 c.c.), then passed through a narrow water-condenser and three bubblers (*a*, *b*, and *c*), wrapped in black paper and each containing 1 : 1 carbon tetrachloride–chloroform (20 c.c.) at −78°. The olefin trapped in *a* and *b* was estimated at certain times by the method of Cooper, Hughes, and Ingold.[3] In no case did olefin reach *c*. The first-order rate constants and infinity titres were calculated by Guggenheim's method.[7]

Hydrolyses. Ethanol (8 vols.) was mixed with the ester, and hydrochloric acid (2 vols.) added to produce a 0·1 or 1N-solution. The runs were followed as described [3] in Part I. In the case of *tert.*-butyl benzoate the integrated first-order rate constants fell during the reaction, $k_1^{(0\cdot25)}/k_1^{(0)}$ being *ca.* 0·9. This is doubtless due to esterification of benzoic acid, as k_1/C_A for loss of benzoic acid in 80% ethanol is $2{\cdot}8 \times 10^{-4}$ min.$^{-1}$ l. mole^{-1} at 50° in 1 and 0·1N-hydrochloric acid for an initial concentration of 0·14M. The rate constants were obtained by extrapolation to zero reaction.

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[*Received, March 28th,* 1956.]

[4] Long and Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3267; Paul, *ibid.*, 1952, **74**, 141; Taft, *ibid.*, p. 5372; McIntyre and Long, *ibid.*, 1954, **76**, 3240; Bell and Brown, *J.*, 1954, 774; Bunton, Konasiewicz, and Llewellyn, *J.*, 1955, 604; Gold and Hilton, *J.*, 1955, 843.

[5] Long, McDevit, and Dunkle, *J. Phys. Chem.*, 1951, **55**, 829; Bell, Dowding, and Noble, *J.*, 1955, 3106.

[6] Braude and Stern, *J.*, 1948, 1978.

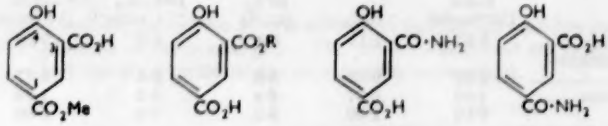
[7] Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

903. *The Partial Hydrolysis of Dialkyl Esters of 4-Hydroxyisophthalic Acid.*

By J. M. Z. Gladych and E. P. Taylor.

It has been shown by Hunt, Idris Jones, and Lindsey [1] that Fischer–Speier esterification of 4-hydroxy*iso*phthalic acid yields diesters together with small amounts of the corresponding monoesters; the orientation of the monomethyl ester so obtained was established as (I). The same authors have also shown that partial hydrolysis of the dimethyl ester by potassium hydroxide in boiling aqueous methanol yields the same monomethyl ester (I).

We have confirmed these results, but have found that hydrolysis of dialkyl 4-hydroxy-*iso*phthalates with excess of aqueous sodium hydroxide at room temperature gives the isomeric monoalkyl ester (II). This has been effected with the dimethyl, diethyl, and di-*n*-propyl esters. In addition to the fact that the resulting monoesters were different from those obtained by Hunt *et al.*, their structure is confirmed by their ammonolysis to the known mono-3-amide [2] (III).



(I) (II) (III) (IV)

The di-*n*-butyl ester appeared to form a sodium salt which was very sparingly soluble in water and resisted hydrolysis with aqueous alkali, regenerating the original ester on acidification. This salt, however, when refluxed with 50% aqueous methanol for 3 hours (without the addition of more alkali), gave the 1-monobutyl ester in good yield; the orientation was confirmed by ammonolysis to the known mono-1-amide [2] (IV).

Experimental.—Partial hydrolysis of dialkyl esters (general method). The dialkyl ester was dissolved in 0·5N-aqueous sodium hydroxide and kept at room temperature for 2—3½ hr. (see Table 1). The pH was then adjusted to 8·4—8·7 with 2N-hydrochloric acid. Any unchanged dialkyl ester was filtered off, washed with water, dried, and identified by m. p. and mixed m. p. determinations. [The di-*n*-propyl ester, which separated as a liquid, was extracted with benzene, the extract washed with water, the solvent recovered, and the identity confirmed by refractive index determination (n_D^{22} 1·5105).] The filtrate obtained after removal of the dialkyl ester was then acidified with 2N-hydrochloric acid to pH 4·8—5·0, and the resulting 3-monoalkyl ester was filtered off, washed with water, and dried. Acidification of the filtrate to Congo-red yielded 4-hydroxy*iso*phthalic acid. The results are in Table 1.

Table 1. *Hydrolysis with aqueous alkali at room temperature.*

Ester	Molar ratio, NaOH : ester	Time (hr.)	Yield (%) of crude product: Unchanged dialkyl ester	3-Monoalkyl ester	Acid
Me_2	2 : 1	2·5	42	23·5	29
Me_2	3 : 1	2·0	11	42	30
Me_2	4 : 1	2·0	2·5	38·5	55
Me_2	4 : 1 *	2·0	7	38	50
Et_2	4 : 1	2·0	6	50·5	35
Pr^n_2	4 : 1	2·0	38	25	36
Bu^n_2	4 : 1	3·5	82	—	10

* KOH used in this experiment.

Hydrolyses in aqueous methanol are recorded in Table 2.

Paper electrophoresis in 2N-acetic acid of a sample of the crude hydrolysis product of the dimethyl ester (obtained by complete acidification of the reaction mixture) indicated that the

[1] Hunt, Idris Jones, and Lindsey, *J.*, 1956, 3099.
[2] *Idem, Chem. and Ind.*, 1955, 417.

1-monomethyl ester was formed in very small quantity when the molar ratio of alkali to ester was not more than 3 : 1.

The following 3-monoalkyl esters (crystallised from alcohol) of 4-hydroxy*iso*phthalic acid are new: 3-*Methyl*, needles, m. p. 253—254° (Found: C, 54·8; H, 3·9. $C_9H_8O_5$ requires

TABLE 2. *Hydrolysis of dimethyl* 4-*hydroxy*iso*phthalate with* 1·5% *of alkali in boiling* 50% *aqueous methanol for* 3 *hours.*

Molar ratio, alkali : ester	Yield (%) of crude product: 1-Monoalkyl ester	Acid	Molar ratio, alkali : ester	Yield (%) of crude product: 1-Monoalkyl ester	Acid
3·75 : 1 (KOH)	—	91	1·57 : 1 (NaOH)	—	97
* 1·12 : 1 ,,	78	—	1·12 : 1 ,,	73	—

* Proportions used by Hunt *et al.*[1]

C, 55·1; H, 4·1%). 3-*Ethyl*, needles, m. p. 205—205·5° (Found: C, 57·1; H, 4·6. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). 3-n-*Propyl*, prisms, m. p. 171—171·5° (Found: C, 58·9; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

Confirmation of structure. The monoalkyl ester (2 g.) and aqueous ammonia (*d* 0·880.; 10 ml.) were heated in a sealed tube at 110—115° for 4·5 hr. After concentration to drive off the bulk of the ammonia, the residue was cooled and acidified with 2N-hydrochloric acid to Congo-red, and the resulting mono-3-amide filtered off, washed with water, and dried. Yields of crude amide, m. p. 296° (decomp.) (lit.,[2] 297°), exceeded 90%. After recrystallisation from aqueous dimethyl formamide, the m. p. rose to 297° (decomp.) (Found: C, 52·6; H, 3·9; N, 7·8. Calc. for $C_9H_7O_4N$: C, 53·1; H, 3·9; N, 7·7%).

The 1-n-*butyl* 3-*hydrogen* 4-*hydroxy*iso*phthalate* crystallised from aqueous methanol as needles, m. p. 141—142° (Found: C, 60·5; H, 5·8. $C_{13}H_{14}O_5$ requires C, 60·5; H, 5·9%). On ammonolysis, this gave an excellent yield of the mono-1-amide, m. p. and mixed m. p. 276° (decomp.) [lit.,[2] 275° (decomp.)].

We are grateful to Mr. S. E. Hunt, Dr. J. Idris Jones, and Dr. A. S. Lindsey of the Chemical Research Laboratory, Teddington, for communicating their results before publication. We thank the Directors of Messrs. Allen & Hanburys Ltd. for permission to publish this note.

RESEARCH DIVISION, ALLEN AND HANBURYS LTD.,
WARE, HERTS.

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904. *Compounds Derived from Cholestenone.*

By G. D. MEAKINS and O. R. RODIG.

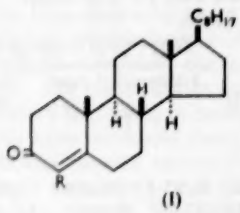
IN work concerned with ring A of the steroids we required derivatives of cholestenone with substituents at position 4. This note describes the preparation of 4-methyl- (I; R = Me) and 4-2′-carboxyethyl-cholest-4-en-3-one (I; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$).

Preliminary experiments showed that the methyl compound could not be prepared satisfactorily by direct methylation of cholestenone (I; R = H),[1] and attention was turned to a method based on the enol-lactone [2] (III). Conversion of this compound into cholestenone by treatment with methylmagnesium iodide and cyclisation of the resulting diketone is well known: [3] the use of ethylmagnesium iodide led to the required methylcholestenone (I; R = Me).

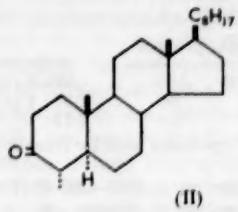
Reduction of the conjugated ketone with lithium in liquid ammonia produced 4α-methylcholestan-3-one (II), which had been prepared previously by methylation of cholestanone derivatives.[1] Hydrogenation in acetic acid resulted in the rapid uptake of two mols. of hydrogen, and chromic acid oxidation of the product gave a mixture of ketones from which a small quantity of the saturated ketone (II) was isolated. Presumably the 4α-methyl compound arises by isomerisation of the 4β-methyl derivative which was expected as the product of *cis*-addition of hydrogen to the 4 : 5-bond.

[1] Beton, Halsall, Jones, and Phillips, unpublished work.
[2] Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579.
[3] Fujimoto, *ibid.*, 1951, **73**, 1856, and later papers.

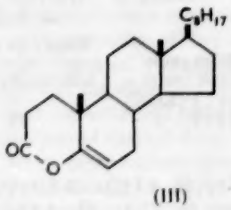
The keto-acid (I; R = $CH_2 \cdot CH_2 \cdot CO_2H$) was obtained by addition of methyl acrylate to cholestenone in the presence of potassium *tert.*-butoxide and subsequent hydrolysis. Later experiments showed that extensive hydrolysis occurs during the acrylate addition and that the acid can be isolated directly in 40% yield.



(I)



(II)



(III)

Experimental.—Rotations were measured in $CHCl_3$. J. Crosfield's silica, " Woelm " alumina, and light petroleum (b. p. 60—80°) were used for chromatography.

4-Methylcholest-4-en-3-one.—Ethylmagnesium iodide was prepared under nitrogen by refluxing ethyl iodide (3·3 g.) in ether (80 c.c.) with magnesium (0·8 g.) for 1·5 hr., and the concentration of the solution was determined by titration with standard hydrochloric acid. A portion (*ca.* 19 c.c.; 0·73 g. of ethylmagnesium iodide) was added to a solution of the enol-lactone (1·5 g.) in ether (15 c.c.) at 0° under nitrogen. The mixture was kept at 0° for 13 hr., acidified with 6N-hydrochloric acid, and extracted with ether. The residue obtained after the removal of ether was refluxed in methanol (60 c.c.) for 3 hr. under nitrogen with a solution of sodium hydroxide (2·05 g.) in water (10 c.c.). Concentration, dilution with water, and extraction with ether yielded an oil (1·3 g.) which was dissolved in benzene and adsorbed on alumina (50 g.). The product eluted with benzene (300 c.c.) crystallised from methanol, to give 4-methylcholest-4-en-3-one (1·06 g.), m. p. 94—98°. Recrystallisation afforded material (0·75 g.), m. p. 102—103°, $[\alpha]_D$ −108° (*c*, 0·9) (Found: C, 84·45; H, 11·5. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%), light absorption max. in EtOH at 2500 Å (ε 15,600), $\nu_{max.}$ 1671 cm.$^{-1}$ in CS_2.

Reduction of 4-Methylcholest-4-en-3-one.—(*a*) The methylcholestenone (190 mg.) in dry ether (35 c.c.) was added slowly to a stirred solution of lithium (100 mg.) in liquid ammonia (75 c.c.). After 20 min. ammonium chloride was added, the ammonia was allowed to evaporate, and the mixture was worked up by dilution with water and ether-extraction. The product (190 mg.) was chromatographed from benzene on alumina (20 g.). Benzene–ether (19 : 1; 150 c.c.) eluted an oil (130 mg.) which crystallised from methanol to give 4α-methylcholestan-3-one (102 mg.), m. p. and mixed m. p. 123—124°, $[\alpha]_D$ +26° (*c*, 1·1), $\nu_{max.}$ 1708 cm.$^{-1}$ in CS_2.

(*b*) A solution of methylcholestenone (500 mg.) in glacial acetic acid (10 c.c.) was shaken with Adams catalyst (150 mg.) in hydrogen for 1 hr. (uptake, 98 c.c.). The residue obtained after removal of catalyst and solvent was oxidised in acetone (40 c.c.) with 8N-chromic acid. The product (420 mg.) was adsorbed from light petroleum on alumina (40 g.). The fractions eluted with light petroleum–benzene and with benzene (100 c.c.) were discarded. Elution with benzene–ether (49 : 1; 250 c.c.) gave an oil (210 mg.) which, after three crystallisations from methanol, yielded 4α-methylcholestan-3-one (85 mg.), m. p. 120—122°, identified as above.

4-2′-Carboxyethylcholest-4-en-3-one. (*a*) A M-solution of potassium *tert.*-butoxide in *tert.*-butyl alcohol (7 c.c.) was added under nitrogen to a stirred solution of cholestenone (2 g.) in ether (20 c.c.). After 15 min. the mixture was cooled to 0°, and freshly distilled methyl acrylate (0·6 g.) in ether (10 c.c.) was added during 5 min. Stirring was continued for 1·5 hr. at 0°, then for 1 hr. at 20°. Water (5 c.c.) was added, the organic solvents were removed under reduced pressure, and the residue was refluxed under nitrogen for 2·5 hr. with potassium hydroxide (10 g.) in 50% aqueous methanol (60 c.c.). The mixture was concentrated *in vacuo*, diluted with water, and washed with ether. Acidification with hydrochloric acid and extraction with ether gave an oil (2·1 g.). A small part of this oil was chromatographed on silica gel. Benzene–ether (4 : 1) eluted material which crystallised on titration with acetone. These crystals were used as seeds in the crystallisation from acetone of the main part of the product. The *keto-acid* was obtained as plates (1·3 g.), m. p. 136—138°, $[\alpha]_D$ −88° (*c*, 1·0) (Found: C, 78·8; H, 10·6. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%), light absorption max. in EtOH at 2500 Å (ε = 14,200), $\nu_{max.}$ 1714, 1672 cm.$^{-1}$ in CS_2.

(*b*) The preceding experiment was repeated as far as the addition of water (5 c.c.). The organic layer was separated and extracted with aqueous sodium hydrogen carbonate. Acidification of the alkaline solution and extraction with ether afforded the keto-acid (0·94 g.), m. p. 135—137°.

THE UNIVERSITY, MANCHESTER, 13. [*Received, June 22nd,* 1956.]

905. *The Preparation and Manipulation of Molybdenum Hexafluoride.*

By T. A. O'DONNELL.

ALTHOUGH there are several reports of the preparation of molybdenum hexafluoride by direct fluorination of the metal, it is not generally recognised that the compound can be prepared, and its physical and chemical properties studied, in relatively simple vacuum-apparatus. Thus the original preparation [1] was performed in platinum and several authors refer to nickel–copper or Teflon systems.[2] Gaunt [3] describes the storage in glass at −80° of a purified sample used for structural analysis and the handling of the sample in an all-glass apparatus which had been exhaustively dried beforehand and in which a fully fluorinated tap-grease was used. However, his system was very different from those needed for most chemical investigations. Preparation of the hexafluoride is usually accompanied by the formation of hydrogen fluoride and reaction of the latter with glass leads to autocatalytic hydrolysis of the hexafluoride. In the present work the product was collected in glass traps which had been carefully cleaned and " flamed " *in vacuo* and to which sodium fluoride was added as a " getter " for the hydrogen fluoride. The hexafluoride could then be purified and stored in glass break-seal tubes, as Gaunt states; but prolonged manipulation of the hexafluoride and its reaction products in glass systems with greased taps and joints was found to be impossible even though fluorinated greases were used. This was due presumably to the difficulty of drying the systems adequately. Conventional greased taps and tapered joints have been replaced by specially designed valves and joints.

The techniques described here for the handling of molybdenum hexafluoride could be applied to other volatile reactive fluorides.

Experimental.—The reaction between fluorine and metallic molybdenum, which had been previously heated in hydrogen and cooled in nitrogen, was performed in a copper tube, and the product was collected in a series of three glass traps. Each trap was provided with a break-off seal and between each was a capillary constriction. Initially, powdered sodium fluoride was added to the clean dry traps, which were then flamed while connected to a high-vacuum system. Dried air was admitted before connection of the traps to the copper tube. The reaction was initiated at about 100° and then became self-sustaining. Most of the hexafluoride, together with the less volatile oxyfluoride which was also formed, condensed in the first trap at −78°. The other two traps were maintained at −196° as guard traps. There was considerable loss of hexafluoride as " smoke " if the first trap was at −196°. When reaction was complete, excess of fluorine was swept from the system with dry nitrogen, and the trap at −78° was sealed off.

This trap was then joined through its break-off seal with a system of several break-seal traps in series, the latter system being connected through a capillary tube to a pumping system. These traps were flamed *in vacuo* but no " getter " was added. The crude hexafluoride was cooled to −196° and the seal broken. Residual nitrogen in the system was pumped away and the capillary tube between the traps and the pumping system was sealed, providing an all-glass greaseless system. The first of the clean traps was then cooled to −78° and the last to −196°. The crude hexafluoride was allowed to distil at room temperature, almost all of the hexafluoride being deposited as colourless crystals in the trap at −78°. Small amounts of silicon tetrafluoride from the preparation condensed in the trap at −196°, and the sodium fluoride " getter " and the relatively involatile molybdenum oxyfluoride remained in the original trap. The first

[1] Ruff and Eisner, *Z. anorg. Chem.*, 1907, **52**, 256.
[2] Burke, Smith, and Neilson, *J. Chem. Phys.*, 1952, **20**, 447.
[3] Gaunt, *Trans. Faraday Soc.*, 1953, **49**, 1122.

and last traps were sealed off and the pure hexafluoride was distributed equally by distillation between the remaining traps to give samples of convenient size. These samples could be stored indefinitely in glass at room temperature without sodium fluoride. They underwent no visible change and no silicon tetrafluoride was formed after three months. The reactions of the hexafluoride are being studied by using similar techniques.

Molybdenum hexafluoride was characterised by its m. p. and molecular weight. The m. p. was 17·4° in a sealed trap, in agreement with the value of 17·5° given by Ruff and Ascher.[4] However, since the compound reacts with mercury and with grease, the conventional apparatus for determination of molecular weights by the Dumas method, in which greased taps and joints are used, was modified. Glass taps in the manifold of the vacuum-system were replaced by metal valves. To each end of a Hoke valve No. 431, a brass-bodied valve with stainless-steel needle and bronze bellows was silver-soldered a copper–Pyrex seal (General Electric Co.'s thimble SE5), and the valves so made were resistant to reactive fluorides and maintained a vacuum for pressures down to 10^{-3}—10^{-4} mm. Hg. Instead of a mercury manometer's being used, a sensitive Pyrex spiral gauge was sealed directly to the manifold. A mirror was fitted to the spiral, and the gauge was used as a null-point instrument. The molecular-weight bulb, of about 350 ml. capacity and as light as possible, was connected by a copper–Pyrex seal to one end of a Hoke valve, which had been stripped of excess of metal, and to the other end was silver-soldered a B14 brass cone. The vacuum-seal between this cone and a B14 glass socket on the manifold was made by a tapered Teflon sleeve lightly smeared on its upper edge with a completely fluorinated hydrocarbon grease.

The molecular weight was determined in the usual way, except that, since it is inadvisable to flame the spiral gauge, the whole system was flushed several times before and after the determination with dry air to ensure that no moisture entered the system. If this were to happen, the gauge and bulb would be contaminated with hydrolysis products and the valves would be corroded. It was found that virtually all of the sample could be recovered after a determination and values of 211 and 212 (calc., 210) were obtained for the hexafluoride.

The author, who carried out this work while on leave from the University of Melbourne, thanks Professor H. J. Emeléus for advice and the Officers of the Royal Society for the award of a Royal Society and Nuffield Foundation Commonwealth Bursary.

University Chemical Laboratory,
Pembroke Street, Cambridge. [*Received, January 16th*, 1956.]

[4] Ruff and Ascher, *Z. anorg. Chem.*, 1931, **196**, 146.

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906. *Vapour–Liquid Equilibrium Data for the Benzene–Fluorobenzene System.*

By R. E. Banks and W. K. R. Musgrave.

In view of continued failure to separate mixtures of benzene and fluorobenzene by use of improved fractionating columns, and the well-known propensity of fluorine-containing organic compounds to form azeotropes [1] we investigated the system more closely and have now obtained vapour–liquid equilibrium data which show that no azeotrope formation occurs and, by using Fenske's [2] equation and assuming mixtures of benzene and fluorobenzene to form ideal solutions, we have calculated that 66 theoretical plates would be required to separate a mixture into a distillate containing 99 mole % of benzene and a residue containing 99 mole % of fluorobenzene. In practice this means that such a separation would require about 130 theoretical plates [3] and explains why earlier efforts failed.

The graph of log α against mole fraction of benzene shows that, subject to experimental error, the system is ideal. The average value of α is 1·176 compared with a theoretical value of 1·145.

[1] Evans and Tatlow, *J.*, 1955, 1184.
[2] Fenske, *Ind. Eng. Chem.*, 1932, **24**, 482.
[3] Carney, "Laboratory Fractional Distillation," Macmillan, New York, 1949, p. 40.

EXPERIMENTAL.—"AnalaR" benzene was dried over sodium wire, distilled over fresh sodium wire, and then redistilled through a 60-plate concentric-tube column. A fraction of b. p. 80°/759 mm., n_D^{20} 1·5013, was collected.

Fluorobenzene was dried ($MgSO_4$), distilled, and then redistilled through the concentric-tube column. The fraction of b. p. 84°/760 mm., n_D^{20} 1·4653, was collected.

Mixtures of benzene and fluorobenzene of known composition were prepared by weighing and their refractive indices measured on an Abbé refractometer at 20° ± 0·1°. A composition–refractive index graph was constructed from the results (Table 1).

TABLE 1. *Refractive index–composition data for benzene–fluorobenzene mixtures.*

n_D^{20}	1·4653	1·4690	1·4720	1·4756	1·4818	1·4860	1·4900	1·4944	1·4970	1·5013
Benzene (mole %) ...	—	12·16	20·80	32·0	50·01	61·65	72·33	84·73	91·65	100·00

TABLE 2. *Vapour–liquid equilibrium data.*

Atm. pressure (mm. Hg)	Vapour temp. (° c)	Mole fraction of benzene: liquid	vapour	Atm. pressure (mm. Hg)	Vapour temp. (°c)	Mole fraction of benzene: liquid	vapour
753·8	79·35	1	1	755·5	81·2	0·54	0·57
754·2	79·45	0·97	0·98	754·0	82·1	0·31	0·37
754·2	79·77	0·90	0·92	753·8	82·42	0·25	0·29
754·2	79·8	0·895	0·91	754·2	82·87	0·22	0·24
755·5	80·83	0·63	0·66	753·8	83·5	0·09	0·10
755·5	80·99	0·59	0·63	753·8	84·0	—	—

Vapour–liquid equilibria were determined at atmospheric pressure with a still of the Othmer type,[4] which had a condenser on the outlet tube. No manostat was used but all the experiments were carried out on the same day during which the barometric pressure did not vary by more than 2 mm. The still was charged with 60 ml. of each mixture and maintained at equilibrium, as shown by an N.P.L. thermometer, for 30 min. before samples of distillate and distilland were taken for analysis. The results, from which the b. p.–composition and vapour–liquid equilibrium diagrams were drawn, are given in Table 2.

One of us (R. E. B.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

THE UNIVERSITY, SOUTH ROAD, DURHAM. [*Received, May 30th, 1956.*]

[4] Othmer, *Ind. Eng. Chem. Anal.*, 1932, **4**, 232.

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907. *The Lability of* 1 : 4 : 6-*Triazanaphthalene.*

By ADRIEN ALBERT and CHRISTIAN PEDERSEN.

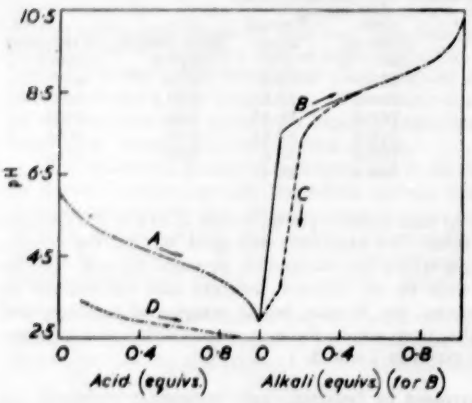
1 : 4 : 6-TRIAZANAPHTHALENE (I) (1-deazapteridine) is unaffected by aqueous alkali, but when it was titrated with acid the potential drifted for about 15 minutes after each addition. The trend was to higher pH, indicating that a stronger base was formed. Whereas curve *D* shows that 1 : 4 : 6-triazanaphthalene is a very weak base of pK_a about 2·5, curve *A*, obtained after equilibration at each addition, corresponds throughout to a stronger base (pK_a 4·52 ± 0·01), which will be called Base A.

When the equilibrated solution was back-titrated with one equivalent of alkali (curve *B*), much higher pH values were obtained, showing that yet another and far stronger base (pK_a 8·53 ± 0·05) had been formed. This will be called Base B, and its formation was almost instantaneous. Curve *B* is of theoretical shape for this pK from the point of 20% neutralization onwards.

Finally, the solution was re-titrated with an equivalent of acid. Instead of duplicating curve *A*, this titration (curve *C*) at first followed curve *B* (for 0·6 equiv. of acid). Thence slightly lower pH values were obtained until 0·8 equiv. of acid had been added. At this stage, the figures showed that about 10% of Base B had disappeared, and the intense mouse-like odour of 1 : 4 : 6-triazanaphthalene became evident. The next 0·1 equiv. of

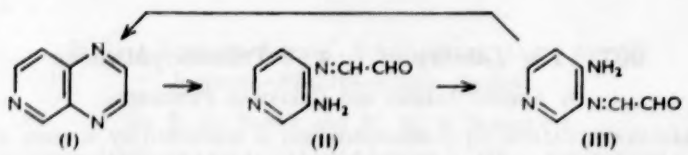
acid caused a sudden drop in pH, and the last two points of curve *C* (at 0·1 and 0 on the abscissa) were first observed about 0·5 pH lower, but within 15 minutes became steady at the values shown. This behaviour suggests that, below pH 8·5, Base B is in rapid equilibrium with 1 : 4 : 6-triazanaphthalene, which is slowly converted into Base A. A weighed quantity of the triazanaphthalene was submitted to three cycles of curves $B + C$, and the same curves were re-traced, showing the absence of side-reactions.

A likely interpretation of these curves is that 1 : 4 : 6-triazanaphthalene is hydrolytically ring-opened by acid, the pyrazine ring (higher N : C ratio) being the more sensitive.[1] Thus Base A with its pK_a of 4·5 should be 3-amino-4-glyoxylideneaminopyridine (II) rather than the isomer (III), because 3-aminopyridine has pK_a 5·98, but 4-aminopyridine is a much stronger base (pK_a 9·17).[2] To examine this matter more fundamentally, 4 : 5-diaminopyridine was titrated and found to have pK_a 9·08 (± 0·01, at 0·05M and 20°) and no



Titration of 1 : 4 : 6-*triazanaphthalene* (0·05M).
A, Titration with N-*hydrochloric acid* (*added by micrometer syringe*) *after* 15 *minutes for equilibration.*
B, Further titration of A *by* 0·1N-*potassium hydroxide.*
C, Further titration of B *with* N-*hydrochloric acid.*
D, As A, *but additions made at* 0·5 *minute intervals.*

second constant above 1·0. Thus the structure of the anil (II) is compatible with a base of about pK_a 5, in so far as the strongly basic nature of 4 : 5-diaminopyridine is due to the vinylogous amidine formed by the ring-nitrogen and the 4-amino-group :[2] in the anil (II),



this amidine is blocked by an electron-attracting group. However the isomeric 4-amino-3-glyoxylideneaminopyridine (III) should be only a little weaker than 4 : 5-diaminopyridine, and hence Base B (pK_a 8·5) would appear to be this isomer. That Base B is not 4 : 5-diaminopyridine was confirmed by paper chromatography. It appears that catalysis by falling drops of alkali during the titration converts (II) into (III). Finally, when neutrality is restored the triazanaphthalene (I) is re-formed. In fact it can be obtained almost quantitatively from a solution of Base B at pH 9 by extraction with ether, or by evaporation, so that the compound (III) must cyclize easily in the absence of water.

Because of the lability of the two anils, they have not yet been obtained in the dry state, or as derivatives. The isomeric 1 : 4 : 6-triazanaphthalene[3] behaved normally on titration

[1] Albert, in "Recent Work on naturally occurring Nitrogen Heterocyclic Compounds," *Chem. Soc. Special Publ.* No. 3, 1955.
[2] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[3] Leese and Rydon, *J.*, 1955, 303.

with acid (pK_a 1·20 ± 0·02). Pteridine gave a steady basic constant, although acid or alkali eventually degraded it to 2-amino-3-formylpyrazine.[4]

1 : 4 : 6-Triazanaphthalene, first prepared in 1936,[5] was more conveniently made as follows. 3 : 4-Diaminopyridine [6] (1 g.), glyoxal hydrate (0·8 g., solid), and alcohol (50 ml.) were refluxed for an hour. The alcohol was removed *in vacuo*, and the residue sublimed at 65°/0·01 mm., then recrystallised from light petroleum, giving 50% of 1 : 4 : 6-triazanaphthalene, m. p. 97° (Found: C, 64·25; H, 3·8; N, 31·4. Calc. for $C_7H_5N_3$: C, 64·1; H, 3·8; N, 32·1%).

1 : 3 : 5-*Triazaindene*.—3 : 4-Diaminopyridine (0·7 g.) was refluxed for an hour with formic acid (1 ml.) and the excess of acid removed *in vacuo*. This gave 52% of 1 : 3 : 5-triazaindene (3-deazapurine), m. p. 168—169°, pK_a (basic) 6·10 ± 0·02, (acidic) 10·88 ± 0·04 (cf. 3·95 and 11·08 for 1 : 3 : 4-triazaindene [6]) (Found: C, 60·55; H, 4·3; N, 34·9. Calc. for $C_6H_5N_3$: C, 60·5; H, 4·2; N, 35·3%). Weidenhagen and Weeden [7] failed to produce the 1 : 3 : 5-isomer similarly, and resorted to a less direct method.

We thank Mr. E. P. Serjeant for the physical measurements.

Department of Medical Chemistry,
Australian National University, Canberra. [*Received, June 27th*, 1956.]

[4] Albert, Brown, and Wood, *J.*, 1956, 2066.
[5] Koenigs, Bueren, and Jung, *Ber.*, 1936, **69**, 2690.
[6] Mason, *J.*, 1954, 2071.
[7] Weidenhagen and Weeden, *Ber.*, 1938, **71**, 2347.

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908. *Oxidation of Organic Compounds by Solid Manganese Dioxide.*

By M. Z. Barakat, M. F. Abdel-Wahab, and M. M. El-Sadr.

Manganese dioxide has been used to oxidise polyene alcohols,[1] steroidal allylic alcohols,[2] benzyl alcohols, and secondary aromatic alcohols [3] to the corresponding carbonyl compounds; in addition three amines have been oxidised to their Schiff bases, an aminoethanol to a lactam, and two hemiacetals to lactones.[4] We have oxidised a wide variety of organic substances with manganese dioxide. The results given in the Table show clearly that the solid cannot be regarded as a specific oxidising agent for particular groupings, *e.g.*, allylic alcohols only.

Hydroxy-compounds, with the exception of triphenylmethanol which did not react, were oxidised to carbonyl compounds, and aromatic aldehydes gave the corresponding carboxylic acids. Polybasic hydroxy-acids, *e.g.*, tartaric acid [5] in ice-cold solution and malic acid in hot solution gave carbon dioxide and acetaldehyde. In these cases it is probable that acetylene is first formed and is hydrated. Hydrogen peroxide was detected by its liberation of iodine from potassium iodide in dilute acetic acid (starch–iodide):

$$HO_2C\cdot[CH\cdot OH]_2\cdot CO_2H + O \longrightarrow C_2H_2 + H_2O_2 + H_2O + 2CO_2$$
$$HO_2C\cdot CH(OH)\cdot CH_2\cdot CO_2H + O \longrightarrow C_2H_2 + 2H_2O + 2CO_2$$
$$C_2H_2 + H_2O \longrightarrow Me\cdot CHO$$

Citric acid yields acetone [6] and malonic acid ethylene, and carbon dioxide. The latter reaction is probably:

$$CH_2(CO_2H)_2 + O \longrightarrow CH_2{:} + 2CO_2 + H_2O$$
$$2CH_2{:} \longrightarrow CH_2{:}CH_2$$

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[1] Ball, Goodwin, and Morton, *Biochem. J.*, 1948, **42**, 516; Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[2] Sondheimer, Amendolla, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 5930, 5932.
[3] Turner, *ibid.*, 1954, **76**, 5175.
[4] Highet and Wildman, *ibid.*, 1955, **77**, 4399.
[5] Cf. Leoncini, *Staz. sper. agr. stat.*, 1910, **43**, 33; *Chem. Zentr.*, 1910, I, 1655.
[6] Cf. Kuyper, *J. Amer. Chem. Soc.*, 1933, **55**, 1722.

α-Hydroxy-acids and α-amino-acids react readily in hot aqueous solution to give the corresponding aldehyde or ketone with one carbon atom less. They all lose carbon dioxide, and amino-acids lose ammonia in addition. Leoncini [7] reported that amino-acids did not give nitric acid with manganese dioxide.

Reactant	Solvent *	Time of reaction (min.)	Yield (%) †	Product.
EtOH	N	20	50	Me·CHO
Pr$^{\alpha}$OH	N	20	50	Me_2CO
Bu$^{\alpha}$OH	N	20	50	Pr$^{\alpha}$·CHO
$(CH_2·OH)_2$	W	20	—	CO_2
$HO·CH(CH_2·OH)_2$	W	20	—	CO_2
Mannitol	W	20	—	CO_2
Inositol	W	20	—	CO_2
Ph·CO·CH(OH)·Ph	C	60	80	Ph·CO·CO·Ph
$C_6H_4(OMe)·CO·CH(OH)·C_6H_4(OMe)$	C	60	52	$C_6H_4(OMe)·CO·CO·C_6H_4(OMe)$
$Ph_2CH·OH$	E	20	88	$(Ph_2·CH)_2O$
„	B	120	87	Ph·CO·Ph
9-Hydroxyxanthene	E	20	91	Xanthone
9-Hydroxyfluorene	E	60	86	Fluorenone
$Ph_3C·OH$	B	120	—	No oxidation ‡
p-$C_6H_4(OH)_2$	E	30	38	p-$C_6H_4O_2$
Ph·CHO	P	24	75	$Ph·CO_2H$
$C_6H_4(OMe)·CHO$	P	24	44	$C_6H_4(OMe)·CO_2H$
o-$C_6H_4(OH)·CHO$	P	24	40	o-$C_6H_4(OH)·CO_2H$
$H·CO_2H$	W	Inst.	—	CO_2
$Ph·CH_2·CO_2H$	W	10	50	Ph·CHO + CO_2 [a]
$(CO_2H)_2$	W	Inst.	—	CO_2
$CH_2(CO_2H)_2$	W	20	—	$C_2H_4 + CO_2$
$HO_2C·CH_2·CH_2·CO_2H$	W	20	—	$C_2H_4 + CO_2$
Maleic acid	W	20	—	$C_2H_2 + CO_2$
Fumaric acid	W	20	—	$C_2H_2 + CO_2$
$HO_2C·[CH(OH)]_2·CO_2H$	W	10	66	Me·CHO + CO_2 [b]
$HO_2C·CH(OH)·CH_2·CO_2H$	W	15	45	Me·CHO + CO_2
Citric acid	W	15	45	Me_2CO
$HO·CH_2·CO_2H$	W	10	—	CO_2
$Me·CH(OH)·CO_2H$	W	10	50	Me·CHO + CO_2
$Ph·CH(OH)·CO_2H$	W	10	50	Ph·CHO + CO_2
$Ph_2C(OH)·CO_2H$	W	30	52	PhCOPh + CO_2 [c]
$H_2N·CH_2·CO_2H$	W	10	—	$CO_2 + NH_3$
$Me·CH(NH_2)·CO_2H$	W	10	—	Me·CHO + CO_2 + NH_3
$Pr^{\alpha}·CH(NH_2)·CO_2H$	W	10	—	Pr^{α}·CHO + CO_2 + NH_3
$Bu^{i}·CH(NH_2)·CO_2H$	W	10	—	Bu^{i}·CHO + CO_2 + NH_3
$HO_2C·CH_2·CH(NH_2)·CO_2H$	W	10	—	Me·CHO + CO_2 + NH_3
$Et·NH_2$	W	15	50	Me·CHO + NH_3
$Ph·NH_2$	P	6 hr.	87	Ph·N:N·Ph
o-$C_6H_4Cl·NH_2$	P	6 hr.	87	o-$C_6H_4Cl·N:N·C_6H_4Cl$-o
p-$C_6H_4Cl·NH_2$	P	6 hr.	87	p-$C_6H_4Cl·N:N·C_6H_4Cl$-p
p-$C_6H_4Me·NH_2$	B	6 hr.	87	p-$C_6H_4Me·N:N·C_6H_4Me$-p
α- or β-$C_{10}H_7·NH_2$	P	24 hr.	—	No oxidation ‡
o-, m-, or p-$C_6H_4NO_2·NH_2$	P	24 hr.	—	No oxidation ‡
Benzophenone hydrazone	E	24 hr.	52	s-Diphenylketazine
Fluorenone hydrazone	E	24 hr.	58	s-Difluorenylketazine
2 : 4-Dinitrophenylhydrazine	B	5 hr.	50	m-$C_6H_4(NO_2)_2$
Ph_2CH_2	P	2 hr.	49	$Ph_2·CH·CHPh_2$ [d]
Ph_3P	P	5 hr.	75	Ph_3PO

* W, water; C, chloroform; E, ether; B, benzene; P, light petroleum (b. p. >120°); N, no solvent.

† Refers to solid or liquid products only.

‡ At least 95% of starting material recovered.

[a] After refluxing, the mixture was cooled, and filtered into ice-cold alcoholic 2 : 4-dinitrophenylhydrazine sulphate solution. [b] Not refluxed. The mixture, cooled in ice, was treated with manganese dioxide, and after 10 min. filtered into ice-cold alcoholic 2 : 4-dinitrophenylhydrazine sulphate solution. [c] After refluxing, the mixture was filtered hot and the residue washed with hot alcohol. Benzophenone separated from the combined filtrates as an oil which solidified on being kept. [d] M. p. 211—212° (from $CHCl_3$) (Found : C, 93·1; H, 6·5. Calc. for $C_{26}H_{22}$: C, 93·4; H, 6·6%).

[7] Leoncini, *Staz. sper. agr. ital.*, 1913, **45**, 224; *Chem. Abs.*, 1913, **7**, 2824.

Aromatic primary amines yielded the corresponding azo-compounds. Previously, however, quinone was obtained from aniline by use of manganese dioxide.[8] Hydrazones yielded the symmetrical diarylketazines. We found that in the oxidation of benzophenone hydrazone, diphenyldiazomethane was an intermediate; it was detected by the violet colour of its ethereal solution.[9]

Experimental.—Water as solvent. The reactant (0·01 mole) and manganese dioxide (B.D.H. Laboratory Reagent, MnO_2 precipitated) (0·05 mole) in distilled water (20—35 ml.) were refluxed in the apparatus described by Schönberg *et al.*[10] in a stream of carbon dioxide. The products were collected in ice-cold alcoholic 2 : 4-dinitrophenylhydrazine sulphate solution. Carbonyl compounds thus precipitated were identified as their 2 : 4-dinitrophenylhydrazones. In separate experiments formation of ammonia or carbon dioxide was tested by use of Nessler's reagent or barium hydroxide solution respectively.

Unsaturated hydrocarbons were detected by decolorising acidified potassium permanganate solution (1/1000) or bromine water. It proved impossible to distinguish between ethylene and acetylene by the copper acetylide test, probably because of simultaneous oxidation of the ammoniacal cuprous chloride solution. However, where acetylene is indicated in the Table, its formation is inferred from the analogous reaction of *N*-bromosuccinimide with maleic and fumaric acids,[11] any other product being unlikely : no acetaldehyde was detected in these cases.

Dry solvents other than ether. The reactant (0·01 mole) and manganese dioxide (0·06 mole) were refluxed in the dry solvent (50 ml.). After filtration the product was isolated by concentration of solvent, except as indicated in the Table, and identified by m. p. and mixed m. p. after recrystallisation.

Ether as solvent. The reactant (0·01 mole), manganese dioxide (0·1 mole), and dry ether were shaken mechanically or allowed to stand with occasional shaking for 24 hr. After filtration, the ether was evaporated off and the product identified by m. p. and mixed m. p. after recrystallisation.

Biochemistry Department, Abbassia Faculty of Medicine,
Ein-Shams University, Cairo. [*Received, April 4th*, 1956.]

[8] Kimijima and Kishino, *J. Soc. Chem. Ind., Japan*, 1944, **47**, 274.
[9] Staudinger and Kupfer, *Ber.*, 1911, **44**, 2197.
[10] Schönberg, Moubacher, and Mostafa, *J.*, 1948, 176.
[11] Barakat, *J. Pharm. Pharmacol.*, 1952, **4**, 582.

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909. *Retardation of the Chain-decomposition of Benzoyl Peroxide by Polycyclic Aromatic Hydrocarbons.*

By J. J. Batten.

During work on the reaction between benzoyl peroxide and phenols [1,2] some observations were made on the relative retarding effects of several polycyclic aromatic hydrocarbons on the chain decomposition of benzoyl peroxide in dioxan solution. Since the observations support the general order of reactivity of the hydrocarbons towards free radicals indicated by other investigations,[3,4,5] and since it is not intended to continue this work, it seems worthwhile placing the results on record (for procedure and analysis see ref. 1; for preparations see ref. 4). The retarding effects of six aromatic hydrocarbons on the decomposition at 80·65° are shown in Fig. 1 in which the amount of peroxide which decomposed in a fixed time is plotted against the initial concentration of hydrocarbon. The effects range from that of diphenyl, which is only just appreciable in the concentration range, to that of anthracene which suppresses the amount of decomposition to a limit. The limit (30%) is only slightly higher than that found under the same conditions for *p*-benzoquinone [1] (28%) or picric acid [2] (27%) as inhibitor and therefore corresponds to almost complete

[1] Batten and Mulcahy, *J.*, 1956, 2948.
[2] Batten, *J.*, 1956, 2959.
[3] Roitt and Waters, *J.*, 1952, 2695.
[4] Kooyman and Farenhorst, *Trans. Faraday Soc.*, 1953, **49**, 58.
[5] Dunn, Waters, and Roitt, *J.*, 1954, 580.

suppression of the chain decomposition. Benzene has no detectable effect at these concentrations, but at higher concentrations is in fact a very weak retarder.[6]

The order of reactivity of the hydrocarbons is : benzene < diphenyl < naphthalene < pyrene < 1 : 2-5 : 6-dibenzanthracene < stilbene < anthracene. This is derived from the results at the high end of the concentration range shown in Fig. 1 : the different order at lower concentrations probably arises from the effects of reaction products. The kinetic behaviour of pyrene, however, appears to be different from that of the other compounds, and it is also anomalous as an antioxidant.[5] The relative reactivities of anthracene and 1 : 2 - 5 : 6-dibenzanthracene are in agreement with the results of Roitt and Waters [3] which were derived from analyses of the products. The order of reactivity of the seven hydrocarbons towards the radicals involved in this reaction thus agrees with that found by Kooyman and Farenhorst [4] for the reactivity towards trichloromethyl radicals, except

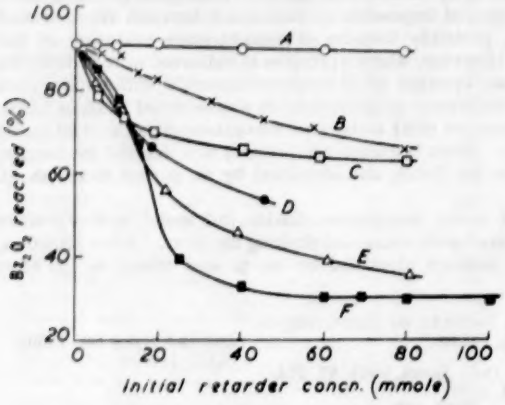

FIG. 1. *Effects of initial concentrations of hydrocarbons on amount of benzoyl peroxide which has reacted in* 135 *min. in dioxan. For Figs.* 1 *and* 2 *initial benzoyl peroxide concn.* = 5 *mmole, and temperature* = 80·65°.

A, Diphenyl; B, naphthalene; C, pyrene; D, 1 : 2-5 : 6-*dibenzanthracene; E, stilbene; F, anthracene.*

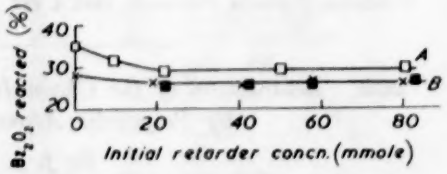

FIG. 2. *Effects of initial anthracene* (□, ■) *and naphthalene* (×) *concentrations on amount of peroxide reacting in* 135 *min. in* (*A*) *acetophenone and* (*B*) *benzene.*

for the position of stilbene which in their results occupies a position between naphthalene and pyrene. To this extent the present results support the conclusions of these authors concerning the influence of structure on the reactivity of polycyclic aromatic hydrocarbons towards free radicals.

There is no evidence of a direct reaction between these hydrocarbons and the peroxide such as occurs with phenols of comparable retarding efficiency.[1,2] This is confirmed by the influence of anthracene and naphthalene on the decomposition in the "unreactive" solvents benzene and acetophenone (Fig. 2). Here again the rate is suppressed to a limit. This presumably corresponds to complete inhibition of the chain reaction which in these solvents occurs to a relatively small extent.

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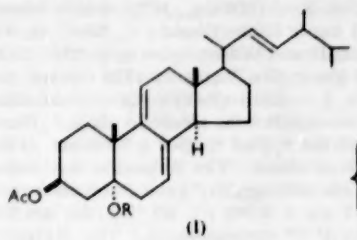
[6] Batten, Thesis, Melbourne, 1955.

910. *Further Experiments on the Epoxidation of Steroids.*

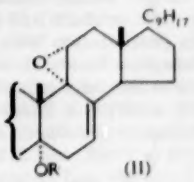
By O. K. Sewell, J. H. Turnbull, and W. Wilson.

The conversion of 5α-hydroxy- and 5α-acetoxy-$\Delta^{7:9:22}$-steroids into 9α : 11α-monoepoxides by reaction with peracids has been discussed in an earlier paper.[1] We now report the isolation of some of the components of the rather complex mixtures produced by epoxidation under more vigorous conditions.

3β-Acetoxyergosta-7 : 9(11) : 22-trien-5α-ol (I; R = H) with performic acid in either "homogeneous" or "heterogeneous" media[2] gave some of the nuclear diepoxide (III; R = H). This was more easily obtained (54% yield) from the 9 : 11-monoepoxide (II; R = H) and excess of monoperphthalic acid; a little triepoxide (IV) was also formed. The latter was readily made from the purified diepoxide and performic acid. Oxidation of the 3 : 5-diacetate (I; R = Ac) with performic acid in heterogeneous media yielded an intractable glass: however, from oxidations in homogeneous media several substances were isolated, including the two diepoxides (III; R = Ac) and (VI), and a substance



(I)



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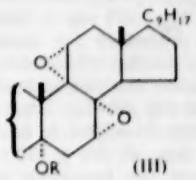

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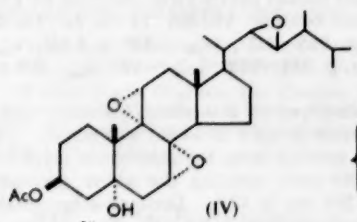

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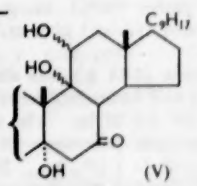

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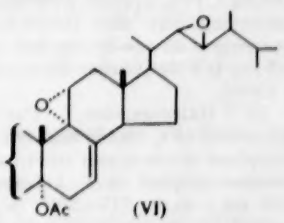
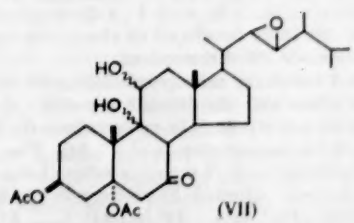


(VI)



(VII)

$C_{32}H_{50}O_8$, which is probably the 9 : 11-dihydroxy-7-oxo-mono-oxide (VII). A related substance $C_{30}H_{48}O_6$, believed to have structure (V), was isolated from the oxidation products of the acetoxy-alcohol (I; R = H) with performic acid in heterogeneous media. Other workers[2,3,4] have isolated 7-oxo-9 : 11-diols similar to (VII) and (V) from the epoxidation products of $\Delta^{7:9}$-steroids. There is considerable chemical evidence[2,4,5] that these substances have the 11α-configuration; however, they are probably formed by way

[1] Burke, Turnbull, and Wilson, *J.*, 1953, 3237.
[2] Cf. Bladon, Henbest, Jones, Wood, Eaton, and Wagland, *J.*, 1953, 2916.
[3] Stork, Romo, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3546.
[4] Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892.
[5] Djerassi, Mancera, Romo, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 3505.

of 7-oxo-9α : 11α-epoxides and, according to the "axial rule" [6] for the fission of steroid epoxides, they should have the 9α : 11β-configuration.

It has been noted [2] that a 5α-acetoxy-group markedly hinders the reaction of a 7 : 8-double bond with peracids. This is consistent with our results, which indicate that in the 5α-acetoxy-series, side-chain epoxidation may occur in preference to 7 : 8-epoxidation, as in the formation of (VI). The ergosterol side-chain appears to be rather unreactive to peracids, although other workers [7] obtained isomeric side-chain epoxides in low yields from an ergosterol derivative.

Experimental.—Alumina neutralised with acetic acid [8] was used for chromatography; $[\alpha]_D$ are in chloroform. "P.I. Rectified spirit" was used as solvent for the ultraviolet-absorption measurements.

Oxidation of 3β-*acetoxyergosta*-7 : 9(11) : 22-*trien*-5α-*ol*. (*a*) "Homogeneous." The triene (1·16 g.) in dioxan (360 c.c.) was added to a mixture of 99% formic acid (11 c.c.) and hydrogen peroxide solution (34 c.c.; 100-vol.). After 18 hr. at 25° the solution was poured into water and the product isolated by means of ether. Chromatography gave benzene–light petroleum eluates containing 3β-acetoxy-7α : 8α-9α : 11α-diepoxyergost-22-en-5α-ol (120 mg., 10%), which formed needles, m. p. 223—228°, $[\alpha]_D$ −10° (*c* 0·81), $\lambda_{max.}$ 207 mμ (ε 1300) (Found: C, 74·0; H, 9·4. Calc. for $C_{30}H_{46}O_5$: C, 74·05; H, 9·55%); Burke, Turnbull, and Wilson [1] give m. p. 234—235°, $[\alpha]_D$ −10°, $\lambda_{max.}$ 203 mμ (ε 1020). The product had absorption bands at 1728 (acetyl) and 3600 cm.$^{-1}$ (hydroxyl); it gave no precipitation with 2 : 4-dinitrophenylhydrazine solution, and did not develop ultraviolet absorption bands on treatment with alcoholic alkali. Boron trifluoride–ether complex in benzene at 20° for 4 hr. did not appear to give a 7-ketone, as the product did not develop ultraviolet absorption bands in alkali. The diepoxide was boiled for 2 hr. with 2N-sulphuric acid in aqueous dioxan; chromatography gave fractions having absorption max. at 280 (ε 6700), 229 (ε 7700), and 243 mμ (ε 6300) (cf. ref. 1); the last two bands suggest the formation of 7-oxo-Δ^5- and 7-oxo-$\Delta^{5:8(9)}$-chromophores. The diepoxide (160 mg.), 10% aqueous potassium hydroxide (2 c.c.), and dioxan (40 c.c.) were refluxed for 1 hr. Chromatography and recrystallisation from methanol–benzene yielded 7α : 8α-9α : 11α-diepoxyergost-22-ene-3β : 5α-diol as plates (30%), m. p. 245—247°, $[\alpha]_D$ −17° (*c* 1·15), $\lambda_{max.}$ 203 mμ (ε 970) {Burke, Turnbull, and Wilson [1] give m. p. 251—252°, $[\alpha]_D$ −18°, $\lambda_{max.}$ 206 mμ (ε 1200)}.

(*b*) "Heterogeneous." The triene (1·11 g.) was dissolved in chloroform (20 c.c.), and a mixture of 98% formic acid (5 c.c.) and hydrogen peroxide (5 c.c.; 100-vol.) was added. The two-phase mixture was stirred at 20° for 22 hr. The product from the chloroform layer was chromatographed in 1 : 1 benzene–light petroleum (60 c.c.), yielding the above diepoxide (317 mg.), m. p. 217—221°, $[\alpha]_D$ −5° (*c* 1·15), $\lambda_{max.}$ 207 mμ (ε 525). Benzene–ether eluates yielded (?) impure 3β-acetoxy-5α : 9ξ : 11ξ-trihydroxyergost-22-en-7-one (V) (35 mg.), m. p. 186—192°, $[\alpha]_D$ −34° (*c* 0·93) (Found: C, 72·3; H, 9·95. Calc. for $C_{30}H_{48}O_6$: C, 71·4; H, 9·6%). This product gave a yellow precipitate within 2 hr. with 2 : 4-dinitrophenylhydrazine solution; ethanolic potassium hydroxide at 20° for 16 hr. developed an absorption band at 250 mμ (ε 6700), attributable to the formation of a 7-oxo-$\Delta^{5:8(9)}$-chromophore.

(*c*) Oxidation of the triene with 1·1 mols. of monoperphthalic acid in ether gave a product which contained 10% of unchanged triene and was difficult to purify. 1·3—1·4 Mols. of monoperphthalic acid gave 60% yields of 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-dien-5α-ol.

3β-*Acetoxy*-7α : 8α-9α : 11α-22 : 23-*triepoxyergostan*-5α-*ol*. (*a*) The above monoepoxide (0·63 g.) was treated with monoperphthalic acid (2 mols.) in ether (140 c.c.) at 20° for 11 days. Recrystallisation from methanol–benzene afforded 3β-acetoxy-7α : 8α-9α : 11α-diepoxyergost-22-en-5α-ol (124 mg., 19%), m. p. 212—219°, $[\alpha]_D$ −12° (*c* 1·34), $\lambda_{max.}$ 202 mμ (ε 1200) (Found: C, 73·5; H, 9·55. Calc. for $C_{30}H_{46}O_5$: C, 74·05; H, 9·55%). The mother-liquors were evaporated and chromatographed. A benzene–ether eluate was recrystallised from methanol–benzene, to afford 3β-*acetoxy*-7α : 8α-9α : 11α-22 : 23-*triepoxyergostan*-5α-*ol* (39 mg.), m. p. 216—224°, $[\alpha]_D$ −7° (*c* 0·7), $\lambda_{max.}$ 202 mμ (ε 375) (Found: C, 71·75; H, 9·0. $C_{30}H_{46}O_6$ requires C, 71·7; H, 9·2%). The triepoxide developed no ultraviolet absorption bands when treated with alcoholic potassium hydroxide.

(*b*) The diepoxide (252 mg.) was dissolved in chloroform (10 c.c.) and dioxan (60 c.c.), and 98% formic acid (20 c.c.) and hydrogen peroxide (20 c.c., 100-vol.) were added. The mixture

[6] Barton, *J.*, 1953, 1033.
[7] Barton and Laws, quoted by Bladon, Clayton, Greenhalgh, Henbest, Jones, Lovell, Silverstone, Wood, and Woods, *J.*, 1952, 4883.
[8] Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2665.

was left at 20—22° for 4 days. The crude product (230 mg.; m. p. 220—228°) was recrystallised from methanol–benzene, to yield the triepoxide, m. p. 228—231°, $[\alpha]_D$ −5° (*c* 1·13), $\lambda_{max.}$ 203 mμ (ε 530) (Found: C, 71·8; H, 9·0. Calc. for $C_{30}H_{44}O_6$: C, 71·7; H, 9·2%).

Oxidation of 3β : 5α-*diacetoxyergosta*-7 : 9(11) : 22-*triene*. (*a*) The diacetate (640 mg.) with performic acid in aqueous dioxan at 20° for 17 hr. was largely (70%) recovered unchanged; a small amount of 3β : 5α-acetoxyergosta-8(9) : 22-dien-7-one [9] (10 mg.), m. p. 150—153°, $[\alpha]_D$ −29° (*c* 0·24), $\lambda_{max.}$ 250 mμ (ε 6400), was isolated.

(*b*) The diacetate (2·64 g.), dioxan (280 c.c.), 98% formic acid (23 c.c.), and hydrogen peroxide (68 c.c.; 100-vol.) were mixed and left at 25° for 40 hr. The product was chromatographed in benzene–light petroleum (1 : 19). The first eluates (1·4 g.) were rechromatographed and crystallised from methanol, giving 3β : 5α-*diacetoxy*-9α : 11α-22 : 23-*diepoxyergost*-7-*ene* (225 mg.), m. p. 152—154°, $[\alpha]_D$ +50° (*c* 0·64), $\lambda_{max.}$ 207 mμ (ε 6500) (Found: C, 72·5; H, 9·4. $C_{32}H_{48}O_6$ requires C, 72·7; H, 9·15%). This product had no hydroxyl groups (infrared); there was a very weak band at 968 cm.$^{-1}$, probably indicating the presence of a little Δ^{22}-compound as impurity. With alcoholic potassium hydroxide, no ultraviolet absorption bands were developed; however, treatment with 2N-sulphuric acid in aqueous dioxan at 100° for 2 hr. produced a band [$\lambda_{max.}$ 247 mμ (ε 11,000)] attributed to the formation of a 7-oxo-$\Delta^{5:6(9)}$-chromophore [Burke, Turnbull, and Wilson [1] give $\lambda_{max.}$ 246 (ε 11,000)]. Benzene–ether eluates from the chromatogram were rechromatographed and crystallised from methanol, to afford (?) impure 3β : 5α-diacetoxy-22 : 23-epoxy-9ξ : 11ξ-dihydroxyergostan-7-one (VII) (350 mg.), m. p. 207—210°, $[\alpha]_D$ −13° (*c* 0·91), $\lambda_{max.}$ 207 mμ (ε 180) (Found: C, 67·7; H, 8·95. Calc. for $C_{32}H_{50}O_8$: C, 68·25; H, 8·95%), which had infrared absorption at 1728 (acetyl), 3600 ± 50 (OH), and 971 ± 2 cm.$^{-1}$ (Δ^{22}).[10] With alcoholic potassium hydroxide at 80° for 3½ hr., this product developed absorption bands at 231 (ε 11,000) and 272 mμ (ε 4000), attributed to the formation of 7-oxo-Δ^{5}- [$\lambda_{max.}$ 234 mμ (ε 12,500) [11]] and 7-oxo-$\Delta^{5:6(9)}$-chromophores [$\lambda_{max.}$ 272 mμ (ε 14,600) [9]].

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EDGBASTON, BIRMINGHAM, 15.

[*Received, June 20th*, 1956.]

[9] Elks, Evans, Oughton, and Thomas, *J.*, 1954, 463.
[10] Turnbull, Whiffen, and Wilson, *Chem. and Ind.*, 1950, 626.
[11] Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, p. 191.

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911. *The Preparation of Aliphatic Aldehydes and Ketones from Lithium Alkyls and Dimethylamides.*

By E. A. EVANS.

FORMATION of ethylenic aldehydes from lithium alkenyls by *NN*-dimethylformamide has been recently described,[1] and this reaction has now been extended to the lithium alkyl series: $RLi + NMe_2{\cdot}COR' \longrightarrow NMe_2{\cdot}CRR'{\cdot}OLi \longrightarrow CORR' + NHMe_2$ (R′ = H). The aldehydes were obtained in 50—85% yields (see Table), except *iso*valeraldehyde (37%), and for convenience were usually isolated as their 2 : 4-dinitrophenylhydrazones or semicarbazones. However, *iso*propyl-lithium gave no aldehyde, perhaps owing to steric hindrance. ωω′-Dibromoalkanes, $Br{\cdot}[CH_2]_n{\cdot}Br$ (n = 2—5) could not be dimetallated with lithium or cross-metallated with *n*-butyl-lithium.

A number of methyl ketones were similarly prepared by action of *NN*-dimethylacetamide. In general the yields (see Table) were higher than those of the corresponding aldehydes.

R	Yield (%) of R·CHO	Yield (%) of R·COMe	R *	Yield (%) of R·CHO	Yield (%) of R·COMe	R *	Yield (%) of R·CHO	Yield (%) of R·COMe
Et	—	47	Bu^n	52	78	C_8H_{17}	70	—
Pr^n	50	—	C_5H_{11}	67	71	C_9H_{19}	71	—
Pr^i	0	—	C_6H_{13}	85	45	$C_{10}H_{21}$	60	79
Bu^i	37	50	C_7H_{15}	62	—	$C_{11}H_{23}$	—	88

* *n*-Alkyl.

[1] Braude and Evans, *J.*, 1955, 3331.

The reactions of the carboxyamide group with organometallic compounds have also been investigated by Heyns and Pyrus,[2] who found that amides with an excess of a Grignard reagent or with lithium alkyls or aryls give, after hydrolysis, only 20—40% yields of ketones.

Experimental.—M. p.s are corrected. Literature values for m. p.s were taken from " A Textbook of Practical Organic Chemistry " by Vogel, and are given in parentheses after m. p.s.

The lithium alkyls were prepared by Gilman's general procedure[3] in dry oxygen-free nitrogen.

n-Butyraldehyde. *NN*-Dimethylformamide (2 g.) was added dropwise to *n*-propyl-lithium [from Li (0·6 g.) and *n*-propyl bromide (6 g.)] in ether (50 ml.) at −20°. The mixture was stirred for 3 hr. while the solution attained room temperature. The solution was then cooled to −10° and an excess of saturated aqueous ammonium chloride added. After 30 minutes' stirring the ether layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residual liquid was dissolved in methanol (5—10 ml.), and an excess of 2 : 4-dinitrophenylhydrazine in methanol–sulphuric acid added. *n*-Butyraldehyde 2 : 4-dinitrophenylhydrazone (3·5 g., 50% based on dimethylformamide) was separated and crystallised from ethyl acetate–methanol in orange needles, m. p. 123° (123°) (Found : N, 22·4. Calc. for $C_{10}H_{12}O_4N_4$: N, 22·2%).

The following aldehydes R·CHO were similarly prepared. (*a*) As 2 : 4-dinitrophenylhydrazones : R = Bu^n, m. p. and mixed m. p. 98—99° (98°) [free aldehyde, b. p. 102—104° (104°)]; Bu^i, m. p. 121—122° (123°); *n*-C_7H_{15}, m. p. 105—106° (106°); *n*-C_8H_{17}, m. p. 100° (100°); *n*-C_9H_{19}, m. p. 102—103° (104°) (Found : N, 16·5. Calc. for $C_{15}H_{24}O_4N_4$: N, 16·4%); *n*-$C_{16}H_{31}$, m. p. 102—103° (104°) (Found : N, 16·2. Calc. for $C_{17}H_{26}O_4N_4$: N, 16·0%). (*b*) As semicarbazones : R = *n*-C_5H_{11}, m. p. 110—111° (106°) (Found : C, 53·8; H, 9·4. Calc. for $C_{17}H_{15}ON_3$: C, 53·5; H, 9·65%); *n*-C_6H_{13}, m. p. 107° (109°).

Ketones. These were prepared similarly but with *NN*-dimethylacetamide and, except for butanone, were isolated by distillation. M. p. below are those of 2 : 4-dinitrophenylhydrazones, except as stated. R in R·COMe : Et [m. p. and mixed m. p. 114—115° (117°)]; Bu^n, b. p. 68—70°/200 mm. (128°) [m. p. 105—106° (107°)]; Bu^i, b. p. 115—116° (117°) [m. p. 96—97° (95°) (Found: C, 51·4; H, 5·65. Calc. for $C_{12}H_{16}O_4N_4$: C, 51·4; H, 5·7%)]; *n*-C_5H_{11}, b. p. 70°/60 mm. [m. p. 72—73° (89°) (Found : C, 53·65; H, 6·5; N, 18·8. Calc. for $C_{13}H_{18}O_4N_4$: C, 53·4; H, 6·2; N, 19·2%)]; *n*-C_6H_{13}, b. p. 72—74°/30 mm. [m. p. 57—58° (58°) (Found : C, 54·55; H, 6·3; N, 18·3. Calc. for $C_{14}H_{20}O_4N_4$: C, 54·6; H, 6·5; N, 18·2%)]; *n*-$C_{10}H_{21}$, b. p. 150—155°/18 mm. (lit.,[4] 144°/11 mm.) [semicarbazone, m. p. 123° (lit.,[4] 123°) (Found : C, 64·6; H, 10·8; N, 17·0. Calc. for $C_{13}H_{27}ON_3$: C, 64·7; H, 11·2; N, 17·4%)]; *n*-$C_{11}H_{23}$, b. p. 258—262° (lit.,[5] 260—265°) [m. p. 69° (lit.,[5] 69°].

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The Radiochemical Centre, Amersham, Bucks. [*Received, May 7th,* 1956.]

[2] Heyns and Pyrus, *Chem. Ber.*, 1955, **88**, 678.
[3] Gilman and Jones, *Chem. Rev.*, 1954, **54**, 835; cf. Braude, in Chap. 4 of " Progress in Organic Chemistry," Vol. III, Ed. J. W. Cook, Butterworths, 1955.
[4] Krafft, *Ber.*, 1882, **15**, 1708; Pickard and Kenyon, *J.*, 1911, 57.
[5] Guerin, *Bull. Soc. chim. France*, 1903, **29**, 1128; Morgan and Holmes, *J. Soc. Chem. Ind.*, 1925, **44**, 108T; Pickard and Kenyon, ref. 4.

912. *The Preparation and Characterisation of o-Bromophenylmagnesium Bromide.*

By Harry Heaney, Frederick G. Mann, and Ian T. Millar.

We have recently recorded the results of an investigation on the action of magnesium, lithium, and *n*-butyl-lithium in turn on *o*-di-iodobenzene and of a preliminary investigation on the action of these reagents on *o*-dibromobenzene.[1] In view of the more recent publication by Gilman and Gorsich,[2] describing the preparation of *o*-bromophenyl-lithium in 23% yield by the interaction of ethereal *n*-butyl-lithium and *o*-dibromobenzene for 7 minutes at −110°, we now record our extended work on the preparation of *o*-bromophenylmagnesium bromide, which we have obtained by two alternative methods in 26—30% yield.

[1] Heaney, Mann, and Millar, *J.*, 1956, 1.
[2] Gilman and Gorsich, *J. Amer. Chem. Soc.*, 1956, **78**, 2217.

In contrast with certain aromatic *o*-dibromo-compounds such as 3 : 4-dibromotoluene [3] and 1 : 2-dibromonaphthalene,[4] *o*-dibromobenzene resembles 3 : 4-dibromodiphenyl [5] in failing to react with magnesium alone in ether; [1] it fails to give a simple organometallic derivative with lithium in diethyl ether or with *n*-butyl-lithium in light petroleum at ordinary temperatures,[1] and with *n*-butyl-lithium in diethyl ether gives *o*-bromophenyl-lithium only under the special conditions recorded by Gilman and Gorsich.[2] [In these respects it also differs markedly from *p*-dibromobenzene, which gives both mono- and di-(magnesium halides) [6] and the corresponding lithium derivatives.[7]]

We have, however, been able to bring *o*-dibromobenzene into reaction with magnesium in ether by using ethyl bromide as entraining agent, and have studied the effect of variation of the proportion of bromide from 0·2 to 1·0 mol. per mol. of dihalide.

Optimum yields of *o*-bromophenylmagnesium bromide, assessed by the carboxylation method, were obtained by the use of equimolecular proportions of *o*-dibromobenzene and ethyl bromide, *o*-bromobenzoic acid being then obtained in 30% yield and benzoic acid in 8% yield. The latter acid almost certainly arises from the formation of some *o*-phenylenebis(magnesium bromide), which on reaction with carbon dioxide probably forms a chelated complex which on ultimate hydrolysis would give benzoic acid. A comparable mechanism has been suggested for the reaction of *o*-phenylenebis(magnesium iodide) with carbon dioxide, which similarly gives benzoic acid.[1]

Since the presence of both ethylmagnesium bromide and *o*-phenylenebis(magnesium bromide) in the ethereal solutions of *o*-bromophenylmagnesium bromide might prove inconvenient in the synthetic use of the last reagent, an alternative procedure for its preparation has been investigated. We find that *o*-dibromobenzene reacts with magnesium in tetrahydrofuran, in the absence of ethyl bromide, to give *o*-bromophenylmagnesium bromide. However, in this solvent the reagent failed to give any acidic product on attempted carboxylation, and with benzophenone gave only benzpinacol.[8] The Grignard reagent crystallised from tetrahydrofuran at room temperature, and insolubility at the temperature of carboxylation may account for this failure to react normally: on the other hand, no bromobenzene was isolated on subsequent hydrolysis. Our limited experience of tetrahydrofuran indicates that it may often, like dioxan,[9] cause precipitation of Grignard reagents.

We therefore employed iododimethylarsine as a characterising agent,[1] and obtained a 26% yield of *o*-bromophenyldimethylarsine.

Although the yield of *o*-bromophenylmagnesium bromide obtainable by either of the above procedures is not significantly superior to that of *o*-bromophenyl-lithium obtainable at −100°, the necessity for this low temperature of reaction, which results from the exceptionally high reactivity of *o*-halogenophenyl-lithiums,[2] reduces the practical value of this reagent and suggests that *o*-bromophenylmagnesium bromide may be more valuable as a synthetic intermediate.

We are now investigating the use of *o*-bromophenylmagnesium bromide in the preparation of some *o*-bromophenyl- and *o*-phenylenedi-metallic and metalloidal compounds.

Experimental.—Reactions with magnesium were performed under nitrogen in a standard Grignard assembly; carboxylation was carried out by pouring the reaction product on a slurry of solid carbon dioxide and ether. M. p.s were determined on a Kofler stage.

(a) *Preparation in diethyl ether.* A solution of *o*-dibromobenzene (9·45 g.) and ethyl bromide (4·36 g., 1 mol.) in ether (50 ml.) was added dropwise with stirring to magnesium (1·95 g., 2 atom-equivs.) and ether (15 ml.) at such a rate that the solvent did not boil. After 1 hour's

[3] Zalkind, Kirillowa, and Nikiforowa, *J. Gen. Chem.* (*U.S.S.R.*), 1931, **1**, 193.
[4] Zalkind, *Ber.*, 1934, **67**, 1031.
[5] Case, *J. Amer. Chem. Soc.*, 1936, **58**, 1246.
[6] See, *e.g.*, Gilman, Beaber, and Jones, *Rec. Trav. chim.*, 1929, **48**, 597; Weldon and Wilson, *J.*, 1946, 235.
[7] Gilman, Langham, and Moore, *J. Amer. Chem. Soc.*, 1940, **62**, 2327; Gilman and Melvin, *ibid.*, 1950, **72**, 995.
[8] See Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1927, **49**, 236, for other examples of the reduction of ketones to pinacols under comparable conditions.
[9] Schlenk and Schlenk, *Ber.*, 1929, **62**, 920; Noller, *J. Amer. Chem. Soc.*, 1931, **53**, 635.

stirring at room temperature the clear yellow solution was decanted from unchanged magnesium (0·24 g., 12%) and carboxylated. The product was hydrolysed with dilute hydrochloric acid, basified, and extracted with aqueous sodium hydroxide, which when acidified deposited a crude crystalline product, m. p. 130—138° (3·1 g.). Distillation of this product in steam gave benzoic acid, m. p. and mixed m. p. 120° (0·4 g., 8%). The residue on sublimation at 140°/0·1 mm. gave *o*-bromobenzoic acid, m. p. and mixed m. p. 150° (2·4 g., 30%). The ethereal layer on evaporation gave *o*-dibromobenzene, b. p. 94—96°/15 mm. (3·0 g., 31·5%), and an unidentified residue. Reactions performed as above but employing 0·2, 0·4, and 0·6 mol. of ethyl bromide gave respectively 2·2 g., 2·5 g., and 2·8 g. of crude acidic product, m. p. 130—138°; magnesium unreacted, 20%, 14·5%, 13% respectively; *o*-dibromobenzene recovered, 39%, 36%, 34% respectively.

(b) *Preparation in tetrahydrofuran.* Tetrahydrofuran was purified by shaking it with aqueous 40% sodium hydroxide, drying ($CaCl_2$), distilling, and prolonged boiling under reflux over sodium; finally it was distilled from sodium into the reaction vessel. A solution of *o*-dibromobenzene (9·45 g.) in tetrahydrofuran (25 ml.) was added dropwise to magnesium (0·97 g., 1 atom-equiv.) and tetrahydrofuran (15 ml.). Then benzene (20 ml.) was added and the mixture stirred at room temperature for 1 hr.; it was then cooled in ice whilst iododimethylarsine (9·28 g., 1 mol.) in benzene (20 ml.) was added dropwise. The resulting clear yellow solution was stirred for 30 min. and then boiled under reflux for 2 hr. before being cooled in ice and hydrolysed with aqueous ammonium chloride.

The organic layer, when dried and distilled in an atmosphere of nitrogen, gave iododimethylarsine, b. p. 30—40°/1 mm. (1 g., 11%), and *o*-bromophenyldimethylarsine, b. p. 93—98°/1 mm. (2·9 g.). The latter fraction when treated with an excess of methyl iodide deposited *o*-bromophenyltrimethylarsonium iodide, which, once recrystallised from methanol, decomposed without melting at *ca.* 240° (4·35 g., 26%) (Found: C, 26·8; H, 3·2. Calc. for $C_9H_{13}BrIAs$: C, 26·8; H, 3·2%). Jones and Mann [10] record identical behaviour on heating.

Treatment of the methiodide with methanolic sodium picrate gave the corresponding *methopicrate*, m. p. 181—182° (from methanol) (Found: C, 35·5; H, 2·95; N, 8·5. $C_{15}H_{15}O_7N_3BrAs$ requires C, 35·75; H, 3·0; N, 8·35%).

An experiment similar to that described above, but employing a benzene solution of benzophenone (1 mol.) as characterising agent in place of iododimethylarsine, gave a dark red solution which after hydrolysis gave on evaporation of the organic layer a crystalline residue of benzpinacol, which, recrystallised from benzene–light petroleum (b. p. 60—80°), had m. p. and mixed m. p. 182—184° (Found: C, 85·1; H, 6·4. Calc. for $C_{26}H_{22}O_2$: C, 85·2; H, 6·05%). In another experiment, the reaction mixture was carboxylated; no acidic material was isolated from the product, and *o*-dibromobenzene (34%) was recovered. In an experiment in which *o*-bromophenylmagnesium bromide was prepared in tetrahydrofuran at 0°, followed by characterisation with iododimethylarsine as above, the yield of recrystallised *o*-bromophenyltrimethylarsonium iodide fell to 15·5%.

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[10] Jones and Mann, *J.*, 1955, 4472.

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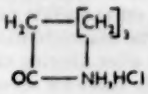
913. *The Beckmann Rearrangement of* cyclo*Pentanone Oxime.*

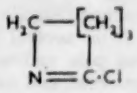
By (MRS.) T. STEPHEN and HENRY STEPHEN.

THE oxime rearranged in chloroform with thionyl chloride to piperid-2-one hydrochloride (I) (47%) and 2-chloro-3 : 4 : 5 : 6-tetrahydropyridine (II) (47%), the yields being in agreement with the mechanism of the Beckmann rearrangement proposed by Stephen and Staskun.[1] Attempts to isolate the pyridine (II) in a pure state were unsuccessful but its formation during the Beckmann rearrangement was established by condensing it with methyl anthranilate to give 6 : 7 : 8 : 9-tetrahydropyrido[2,1-*b*]quinazol-11-one (III).[2]

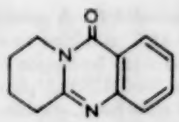
Experimental.—The following improved method gives a 95% yield of *cyclo*pentanone oxime. *cyclo*Pentanone [3] (84 g.) and hydroxylamine hydrochloride (70 g.) in water (250 c.c.) were stirred at room temperature during the addition of sodium hydrogen carbonate (84 g.). The oxime



(I)



(II)



(III)

which crystallised was filtered off, washed with warm water (40°) (150 c.c.), and dried; it was then pure enough for further use.

Rearrangement of the oxime. Thionyl chloride (3·5 c.c.) was added dropwise to the oxime (5 g.) in dry chloroform (100 c.c.) at −5°. The clear green solution was then removed from the freezing mixture; the temperature rose to 15° during the next 5 min., and then rapidly to 38°, its colour changing to yellow with crystallisation of *piperid-2-one hydrochloride*. After being kept at 38° for 5 min. the mixture was cooled at 0° for 30 min., and the hydrochloride filtered off; it crystallised from methanol–ethyl acetate (1 : 1 by vol.) in plates (44%), m. p. 167—169° (decomp.) (Found: Cl, 26·1%; *M*, 140. C_5H_9ON,HCl requires Cl, 26·2%; *M*, 135·5). It also crystallises from thionyl chloride. Piperid-4-one, obtained by rearranging the oxime according to Wallach,[4] was dissolved in chloroform and treated with dry hydrogen chloride, the hydrochloride formed being identical with that described above.

6 : 7 : 8 : 9-*Tetrahydropyrido*[2,1-b]*quinazol*-11-*one* (III). Piperid-2-one hydrochloride (5 g.) was warmed on a water-bath with phosphorus oxychloride (25 c.c.), and after the reaction had subsided the excess of oxychloride was removed under reduced pressure. To the residual oil methyl anthranilate (15 g.) was added and, after the vigorous reaction had ceased, water (150 c.c.) was added, the mixture made alkaline with ammonia, and the excess of methyl anthranilate removed by steam-distillation, leaving an oil which was dissolved in hot dilute hydrochloric acid (charcoal) and filtered. The filtrate, on treatment with ammonia and cooling, deposited white needles (75%) which, recrystallised from hot water, had m. p. 100·5° (Found: C, 72·2; H, 6·2; N, 14·2. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0; N, 14·0%). The *hexachloroplatinate* of the *base* was obtained as orange needles, m. p. 260° (decomp.) [Found: Pt, 24·1%. $(C_{12}H_{12}ON_2)_2,H_2PtCl_6$ requires Pt, 24·1%]. The presence of 2-chloro-3 : 4 : 5 : 6-tetrahydropyridine during the Beckmann rearrangement of *cyclo*pentanone oxime was established as follows: the oxime (4 g., 1 mol.) in chloroform (50 c.c.) was treated as above with thionyl chloride (3 c.c., 1 mol.), and after completion of the rearrangement methyl anthranilate (15 g.) was added, whereupon a vigorous reaction took place with separation of methyl anthranilate hydrochloride, which was removed by filtration. The filtrate was made alkaline with ammonia and stream-distilled to remove chloroform and methyl anthranilate, and the oil remaining was purified as above, yielding needles (40%), m. p. 100·5°, identical with those obtained above.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG. [*Received, May 4th,* 1956.]

[1] Stephen and Staskun, *J.*, 1956, 980.
[2] Stephen and Stephen, *J.*, 1956, 4173.
[3] *Org. Synth.*, 1925, **5**, 37.
[4] Wallach, *Annalen*, 1900, **312**, 179.

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914. *Modification of the Procedure for Converting Nitriles into Aldehydes.*

By (MRS.) T. STEPHEN and HENRY STEPHEN.

THE original method [1] of reducing nitriles to aldehydes assumed the formation of an imidoyl chloride R·CCl(:NH) by addition of hydrogen chloride to the nitrile. Later investigation [2] showed that a nitrilium salt of the type $[R\cdot C{:}NH]^+Cl^-$ is probably formed which then undergoes reduction with stannous chloride. The modification of the procedure is the use of ethyl formate or ethyl acetate as solvent instead of anhydrous ether. The advantage is two-fold; anhydrous stannous chloride and nitriles are readily soluble in both solvents at the ordinary temperature and remain in solution after saturation with hydrogen chloride.

[1] Stephen, *J.*, 1925, 1874.
[2] Hantzsch, *Ber.*, 1931, **64**, 661.

Experimental.—A solution of the nitrile (1 mol.) in ethyl acetate saturated with hydrogen chloride at 0° is added to a solution of stannous chloride (1·1 mol.) in ethyl acetate previously saturated with hydrogen chloride at 0°. After several hours at 0° the stannichloride of the aldimine $[R{\cdot}CH{:}NH_2]^+_2SnCl_6^{2-}$ separates as pale yellow prisms, and after filtering through a sintered glass filter, washing with anhydrous ether, and drying (NaOH *in vacuo* for several days) is analytically pure. To obtain the aldehyde the product after deposition of the stannichloride is completed is poured into water and steam-distilled, which hydrolyses the stannichloride and removes solvent and aldehyde if the latter is volatile in steam (otherwise the aldehyde is extracted from the residue after steam-distillation). The yields of the following aldehydes were almost quantitative, and they were identified by their *p*-nitrophenylhydrazones, 2 : 4-dinitrophenylhydrazones, and semicarbazones. The tin content of the stannichlorides was determined by hydrolysing a weighed sample (0·5 g.) in boiling water (100 c.c.) and then adding ammonia to precipitate stannic hydroxide, which was collected in a weighed crucible, washed with hot water and with ethanol to remove adhering aldehyde, ignited, and weighed. $(Ph{\cdot}CH{:}NH_2)_2SnCl_6$ (Found: SnO_2, 26·9, 27·1. Required: SnO_2, 27·7%). $(m\text{-}Me{\cdot}C_6H_4{\cdot}CH{:}NH_2)_2SnCl_6$ (Found: SnO_2, 26·8. Required: SnO_2, 26·4%). $(p\text{-}Me{\cdot}C_6H_4CH{:}NH_2)_2SnCl_6$ (Found: SnO_2, 26·9. Required: SnO_2, 26·4%). $(\beta\text{-}C_{10}H_7{\cdot}CH{:}NH_2)_2SnCl_6$ (Found: SnO_2, 22·8, 22·7. Required: SnO_2, 23·4%). $[3:4:5\text{-}(MeO)_3C_6H_2{\cdot}CH{:}NH_2]_2SnCl_6$ (Found: SnO_2, 20·6. Required: SnO_2, 20·8%). *p*-Methoxybenzaldehyde, yield 15% after 12 hr.; *p*-tolualdehyde, 30% after 72 hr.; α-naphthaldehyde, 20% after 24 hr.

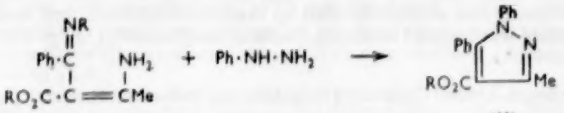
The use of ethyl formate and ethyl acetate as solvents for nitriles in the Hoesch–Houben synthesis of hydroxyaromatic ketones is being investigated.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG. [*Received, May 24th,* 1956.]

915. *The Preparation of Methyl and Ethyl β-Amino-α-(N-substituted-Benzimidoyl)crotonates, and their Conversion into Methyl and Ethyl 3-Methyl-1 : 5-diphenylpyrazole-4-carboxylates.*

By BENJAMIN STASKUN and HENRY STEPHEN.

METHYL and ethyl β-amino-α-(*N*-substituted benzimidoyl)crotonates (I) are readily obtained by the condensation of *N*-substituted benzimidoyl chlorides with methyl and ethyl β-aminocrotonate. On hydrolysis they yield acetophenone, arylamine, and ammonia, which indicate condensation of the benzimidoyl chlorides at the α-carbon of the



(I) (II)

β-aminocrotonic ester. Similar observations were made by Benary [1] and Grob [2] when investigating the action of acid chlorides on ethyl β-aminocrotonate. Evidence for the structure of compounds (I) is also provided by their reaction with phenylhydrazine which affords the 3-methyl-1 : 5-diphenylpyrazole-4-carboxylates (II). Further, all the methyl esters (I) yield the same methyl ester (II; R = Me), and the ethyl esters yield the ethyl ester (II; R = Et).

Experimental.—General procedure for the condensation of imidoyl chlorides with β-aminocrotonic esters. The ester (0·01 mol.) in dry chloroform (40 c.c.) is treated with the imidoyl chloride (0·01 mol.) at 0° for 3—5 days. At this temperature the hydrogen chloride liberated does not attack the ester. Condensation proceeds slowly, as indicated by the development of a yellow colour in chloroform, and when there is no further change 5% hydrochloric acid (20 c.c.) is added and the chloroform removed by steam-distillation. The aqueous residue is chilled and filtered; the yellow filtrate, after being made alkaline with ammonia, deposits the crude base which crystallises from dilute methanol or ethanol (charcoal). The new compounds are more basic than the β-aminocrotonic esters and are present in the chloroform solutions as the yellow hydrochlorides. The latter are also prepared by passing hydrogen chloride through a chloroform solution of the bases. *Products* are tabulated.

[1] Benary, *Ber.*, 1909, **42**, 3912; Benary *et al.*, *Ber.*, 1917, **50**, 65.
[2] Grob, *Helv. Chim. Acta*, 1950, **33**, 1787.

R in Ph·CCl:NR	X in NH_2·CMe:CH·CO_2X	Product (I)	Yield (%)	M. p.	Found: N (%)	Reqd.: N (%)
Ph	Me	$C_{18}H_{18}O_2N_2$ *	67	144°	9·65	9·5
	Et	$C_{19}H_{20}O_2N_2$ *	64	101	9·2	9·1
o-Tolyl	Me	$C_{19}H_{20}O_2N_2$ *	73	156	8·9	9·1
	Et	$C_{20}H_{22}O_2N_2$ *	24	101	8·45	8·7
m-Tolyl	Me	$C_{19}H_{20}O_2N_2$ *	55	127	9·0	9·1
p-Tolyl	Me	$C_{19}H_{20}O_2N_2$ *	73	159	9·1	9·1
o-Xylyl	Me	$C_{20}H_{22}O_2N_2$ *	88	163	8·8	8·7
	Et	$C_{21}H_{24}O_2N_2$	84	176	8·3	8·3
α-Naphthyl	Me	$C_{22}H_{20}O_2N_2$ *	52	174	8·35	8·1
β-Naphthyl	Et	$C_{23}H_{22}O_2N_2$ *	50	141	8·0	7·8
Me	Me	$C_{13}H_{16}O_2N_2$	38	137	12·0	12·1
Et	Me	$C_{14}H_{18}O_2N_2$	68	105	11·3	11·4
	Et	$C_{15}H_{20}O_2N_2$	75	107	10·6	10·8
N-3 : 4 : 5-Trimethoxyphenylbenzimidoyl chloride	Me	$C_{21}H_{24}O_5N_2$	26	171	7·45	7·3
	Et	$C_{23}H_{28}O_5N_2$	35	154	6·8	7·0

* These compounds are yellow needles from methanol or ethanol; others are colourless needles.

Methyl β-N-*acetamido*-α-N-*phenylbenzimidoylcrotonate*. This *ester* was obtained from the base and acetic anhydride. It crystallises in colourless needles (from methanol), m. p. 163° [Found: N, 8·8 (Dumas), 8·6 (Middleton and Stuckey [3]). $C_{20}H_{20}O_3N_2$ requires N, 8·3%]. The *ethyl ester* was similarly obtained as colourless needles (from ethanol), m. p. 123° [Found: N, 8·2 (D.), N, 8·2 (M. and S.). $C_{21}H_{22}O_3N_2$ requires N, 8·0%].

Ethyl N-β-*benzamido*-α-N-*phenylbenzimidoylcrotonate*. The base (0·7 g.) was suspended in 10% aqueous sodium hydroxide (20 c.c.) and treated with benzoyl chloride (2 c.c.) for ½ hr. at room temperature. The *product* crystallises in colourless needles (from dilute ethanol), m. p. 120° (Found: N, 6·9. $C_{25}H_{24}O_2N_2$ requires N, 6·8%).

Hydrolysis. The base (0·5 g.) was refluxed in 70% sulphuric acid (10 c.c.) for ½ hr., cooled, and diluted with water (50 c.c.), and the acetophenone extracted with ether and identified as the 2 : 4-dinitrophenylhydrazone, m. p. 240°. The acidic layer was made alkaline and the amine extracted with ether and in each case identified as the benzoyl derivative.

Methyl 3-*methyl*-1 : 5-*diphenylpyrazole*-4-*carboxylate*. Methyl β-amino-α-*N*-phenylbenzimidoylcrotonate (0·5 g.) and phenylhydrazine (0·2 c.c.) in 50% acetic acid (20 c.c.) were refluxed for 3 hr. and the mixture, after cooling, was treated with water (20 c.c.). The precipitated *pyrazole derivative* crystallised from dilute ethanol (charcoal) in colourless needles, m. p. 132° (Found: N, 9·8. $C_{16}H_{16}O_2N_2$ requires N, 9·6%). The same compound was obtained by treating methyl β-amino-α-*N*-*m*-xylylbenzimidoylcrotonate with phenylhydrazine.

Ethyl 3-*methyl*-1 : 5-*diphenylpyrazole*-4-*carboxylate*. This was prepared by the action of phenylhydrazine on ethyl β-amino-α-*N*-phenylbenzimidoylcrotonate and ethyl β-amino-α-*N*-*o*-tolylbenzimidoylcrotonate. It formed colourless needles (from methanol), m. p. 122° as recorded in the literature.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG. [*Received, May 24th*, 1956.]

[3] Middleton and Stuckey, *J. Pharm. Pharmacol.*, 1951, **3**, 829.

916. *The Preparation and Characterising Constants of the Phenylboron Chlorides.*

By E. W. ABEL, S. H. DANDEGAONKER, W. GERRARD, and M. F. LAPPERT.

FOR investigations of the diphenylboronous (Ph_2BX), and phenylboronic ($Ph{\cdot}BXX'$) series, diphenylboron chloride, Ph_2BCl, and phenylboron dichloride, $Ph{\cdot}BCl_2$, were required in moderate quantities as synthetic intermediates. The methods described herein were developed, which we believe have advantages over earlier ones.

Diphenylboron chloride has previously been prepared, in low yield, by the interaction of diphenylmercury and phenylboron dichloride; [1] it was not characterised. The most recent preparation of phenylboron dichloride involved the interaction of a dialkyl phenylboronate and boron trichloride [2] (for earlier methods, see ref. 3), and subsequent separation of the dichloride from the alkyl dichloroboronite, $RO{\cdot}BCl_2$, formed concurrently. The present method involves the interaction of boron trichloride with the appropriate anhydride in an inert solvent at −80°:

$$(Ph_2B)_2O + BCl_3 \longrightarrow 2Ph_2BCl + BOCl$$
$$Ph{\cdot}BO + BCl_3 \longrightarrow Ph{\cdot}BCl_2 + BOCl$$

[1] Michaelis and Becker, *Ber.*, 1894, **27**, 244.
[2] Brindley, Gerrard, and Lappert, *J.*, 1956, 824.
[3] Lappert, *Chem. Rev.*, 1956, in the press.

The boron oxychloride decomposed to boron trichloride and boron trioxide. The yields obtained were high and the method has the advantage that the required chlorides are the only liquid components. Further, the starting compounds, the anhydrides, are readily accessible. For the previous method of preparing phenylboron dichloride, the dialkyl phenylboronate which was starting material was most conveniently prepared from the anhydride [4] or the acid [4,5] and thus the present method eliminates one step.

Under similar conditions, there was no reaction between boron trifluoride and either anhydride.

Diphenylboronous anhydride was prepared from diphenylboronous acid, obtained by Letsinger and Skoog's method.[6] Physical constants for the acid have not previously been recorded, except for some erroneous early work (see ref. 6). Dehydration to the anhydride was effected at room temperature, by application of a vacuum: previous procedure [6,7] has involved heating (>200°), which we find leads to partial decomposition. Phenylboronic anhydride was obtained similarly by dehydration of the acid, which was obtained by Bean and Johnson's method.[8]

Each of the chlorides was chemically characterised by nearly quantitative hydrolysis to the appropriate anhydride. Phenylboron dichloride was also converted into *n*-butyl phenylchloroboronite, Ph·BCl·OBu, by equimolecular interaction [9] with di-*n*-butyl phenylboronate.

$$2Ph_2B{\cdot}Cl + H_2O \longrightarrow (Ph_2B)_2O + 2HCl$$
$$Ph{\cdot}BCl_2 + H_2O \longrightarrow PhBO + 2HCl$$

The characterising constants of the two chlorides and of diphenylboronous acid are shown in the Table. The value for the refractive index of phenylboron dichloride, quoted previously,[2] shows a misprint in the first decimal place. Both the chlorides were unimolecular, as shown by cryoscopy in *cyclo*hexane under anhydrous conditions with a pulse of dry nitrogen for agitation.[9]

The molecular refractivities for the two chlorides and for diphenylboronous acid are in fair agreement (see Table) with the values calculated from Vogel's data [10] on the phenyl group, hydroxylic oxygen, hydrogen, and chlorine, and Torssell's figures [5] on the atomic refractivity of boron in boronic (for $Ph{\cdot}BCl_2$) and boronous esters (for $Ph_2B{\cdot}Cl$ and $Ph_2B{\cdot}OH$).

Compound	B. p. (°/mm.)	n_D^{20}	d_4^{20}	Found: $[R_L]_D$	Calc.: $[R_L]_D$
$Ph_2B{\cdot}Cl$	98/0·1	1·6118	1·116	62·27	62·03
$Ph{\cdot}BCl_2$	66—66·5/11	1·5430	1·202	41·69	42·41
$Ph_2B{\cdot}OH$	Decomp.	1·5913	1·074	57·25	58·75

Experimental.—Preparation of anhydrides. Diphenylboronous acid (15·9 g.) (Found: C, 77·8; H, 6·0; B, 5·9. $C_{12}H_{11}OB$ requires C, 79·1; H, 6·0; B, 5·9%) was mechanically agitated at 20°/0·005 mm. for 2 hr. The white, crystalline residue (15·01 g., 99%) was diphenylboronous anhydride, which after recrystallisation from *n*-pentane had m. p. 116° (Found: C, 82·9; H, 5·5; B, 6·26. Calc. for $C_{24}H_{20}OB_2$: C, 83·3; H, 5·8; B, 6·24%). Water (0·78 g., 98%) had been evolved and was trapped as a condensate at −80°.

Phenylboronic anhydride, m. p. 218° (Found: B, 10·4. Calc. for C_6H_5OB: B, 10·4%), was obtained by heating the acid at 110—115°/760 mm. for 8—10 hr.

Diphenylboron chloride. Diphenylboronous anhydride (26·0 g., 1 mol.) in methylene dichloride (80 c.c.) was slowly (½ hr.) added to boron trichloride (8·8 g., 1 mol.) in the same solvent (30 c.c.) at −80°. Volatile matter was removed at 20°/10 mm. The resultant mixture comprised a suspension of a white solid, which was filtered off, in a liquid. The filtrate on distillation afforded *diphenylboron chloride* (22·57 g., 76%) (for constants see above) (Found: C, 72·6; H, 5·1; Cl, 17·6; B, 5·4%; *M*, 197. $C_{12}H_{10}ClB$ requires C, 72·0; H, 5·0; Cl, 17·7; B, 5·4%; *M*, 200) as a slightly fuming, colourless liquid.

Water (0·102 g., 1 mol.) in anhydrous diethyl ether (20 c.c.) was added during ½ hr. to the chloride (2·26 g., 2 mols.) in the same solvent (30 c.c.). Volatile matter was removed at 15 mm.

[4] Brindley, Gerrard, and Lappert, *J.*, 1955, 2956.
[5] Torssell, *Acta Chem. Scand.*, 1954, **8**, 1779.
[6] Letsinger and Skoog, *J. Amer. Chem. Soc.*, 1955, **77**, 2491.
[7] Neu, *Chem. Ber.*, 1955, **88**, 1761.
[8] Bean and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 4415.
[9] Brindley, Gerrard, and Lappert, *J.*, 1956, 824.
[10] Vogel, *J.*, 1946, 133; 1948, 616, 644, 654.

The white crystalline solid which remained was washed with *n*-pentane (10 c.c.) and freed from solvent in a vacuum-desiccator. This product was diphenylboronous anhydride (1·87 g., 96%), m. p. 114° (Found : B, 6·3%).

Phenylboron dichloride. Boron trichloride (11·75 g., 1 mol.) at −39° was added dropwise to phenylboronic anhydride (10·10 g., 1 mol.) in methylene dichloride (150 c.c.) at −80°. The mixture was slowly (12 hr.) allowed to attain room temperature. Fractional distillation afforded a fore-run of solvent and then phenylboron dichloride (6·17 g.) (Found : Cl, 44·4; B, 6·9%; *M*, 155. Calc. for $C_6H_5Cl_2B$: Cl, 44·6; B, 6·9%; *M*, 159), as a violently fuming, colourless liquid. The residue contained unchanged anhydride (5·64 g.), m. p. 217—218° (Found : B, 10·4%). The overall yield of phenylboron dichloride was 90%. Substantially similar results were obtained when chloroform, benzene, or *n*-pentane was the solvent and when the molar ratio of anhydride to trichloride was 1·5 : 1. The recovery of unchanged anhydride is probably due to its low solubility.

The dichloride (2·346 g.) was hydrolysed by water (0·27 g.) in the presence of *n*-pentane (10 c.c.). Volatile matter was removed under vacuum. The resultant crystalline residue was washed with *n*-pentane and freed from solvent in a vacuum-desiccator. This product was phenylboronic anhydride (1·45 g., 94·5%), m. p. 217—218° (Found : B, 10·3%).

The dichloride afforded *n*-butyl phenylchloroboronite (92%), b. p. 82°/0·1 mm., $n_D^{29.5}$ 1·4960 (Found : Cl, 17·8; B, 5·5. Calc. for $C_{10}H_{14}OClB$: Cl, 18·0; B, 5·5%), by interaction in equimolecular proportions with di-*n*-butyl phenylboronate.

Lack of reaction between boron trifluoride and the anhydrides. Neither anhydride when dissolved in methylene dichloride (same concentration as for BCl_3 reaction) reacted with boron trifluoride [11] at −80° or at 20°. This was demonstrated by passage of the gas for 1 hr., removal of volatile matter, and quantitative isolation of the appropriate anhydride, which was then characterised.

THE NORTHERN POLYTECHNIC, HOLLOWAY, LONDON, N.7. [*Received, June 8th*, 1956.]

[11] Booth and Willson, *Inorg. Synth.*, 1939, **1**, 21.

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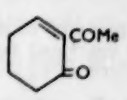
917. *Attempts at the Meyer–Schuster Rearrangement on 2-Ethynyl-2-hydroxycyclohexanone.*

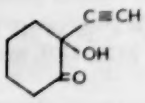
By (Miss) M. E. MCENTEE, A. R. PINDER, HERCHEL SMITH, and R. E. THORNTON.

WE [1] have recently been interested in the problem of preparing 2-acetyl*cyclo*hex-2-en-1-one (I) a much sought-after compound in these laboratories, because of its obvious potentialities as an intermediate in steroid synthesis.[2]

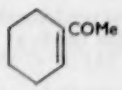
A superficial view might indicate that the alcohol (II) should provide it by a Meyer–Schuster rearrangement (*e.g.*, in formic acid [3] or with an acid-treated ion-exchange resin in acetic acid [4]) or by dehydration to an intermediate enyne followed by hydration of the triple bond. Such processes, which all depend on the readiness with which the carbon atom initially carrying the hydroxyl group becomes cationic,[3,4] will, however, be strongly disfavoured in the compound (II) by the electron-withdrawal from carbon to oxygen in the carbonyl group. Accordingly, our chief efforts to obtain the ketone (I) or its relatives have been directed into other channels.[1,5] However, the ready availability of the alcohol



(I)



(II)



(III)

(II) from *cyclo*hexane-1 : 2-dione and sodium acetylide or the bismagnesium iodide of acetylene has prompted us to study its reaction to Meyer–Schuster conditions.

The alcohol (II) failed to rearrange in formic acid under the Newman conditions [4]

[1] Smith, *J.*, 1953, 803; Pinder and Smith, *J.*, 1954, 113.
[2] Cf. Peak and Robinson, *J.*, 1937, 1581.
[3] Hamlet, Henbest, and Jones, *J.*, 1951, 2652.
[4] Newman, *J. Amer. Chem. Soc.*, 1953, **75**, 4740.
[5] Jaeger and Smith, *J.*, 1955, 646.

or with phosphoric anhydride in benzene.[6] Prolonged heating gave low yields of 1-acetyl-*cyclo*hexene (III) the formation of which in the reactions not involving formic acid, may possibly involve disproportionation.

We have found it convenient to prepare *cyclo*hexane-1 : 2-dione from 2-chloro*cyclo*-hexanone by hydrolysis with boiling water and oxidation with ferric chloride without isolation of the intermediate 2-hydroxy*cyclo*hexanone. The overall yield from *cyclo*-hexanone is higher than that obtained by the standard method,[7] and the process is rapid and avoids the use of selenium dioxide. A similar method has been used to prepare *cyclo*pentane-1 : 2-dione from 2-chloro*cyclo*pentanone.[8]

Experimental.—cyclo*Hexane*-1 : 2-*dione*. 2-Chloro*cyclo*hexanone (90 g.) was refluxed in water (800 c.c.) with stirring until all had dissolved. Ferric chloride (333 g.) in water (167 c.c.) was added during 90 min. and when the solution had cooled to 40° ammonium sulphate (240 g.) was added. Continuous ether-extraction for 6 hr. gave a residue (69 g.), distillation of which gave *cyclo*hexane-1 : 2-dione (33 g., 43%), b. p. 96—100°/24 mm.

2-*Ethynyl*-2-*hydroxy*cyclo*hexanone* (II). (*a*) *cyclo*Hexane-1 : 2-dione (16 g.) in dry ether (25 c.c.) was added during 30 min. with stirring to a solution of sodium acetylide (from the metal, 7 g.) in liquid ammonia (300 c.c.) through which acetylene was passing. The mixture was stirred for a further 2—3 hr., ammonium chloride (16 g.) was added, and the ammonia allowed to evaporate. Water (200 c.c.) was added and the mixture thoroughly extracted with ether. Evaporation of the dried extracts gave an oil (12 g.) which distilled (short Vigreux column) at 104—106°/25 mm. The distillate (9·6 g.) soon solidified; a portion separated from light petroleum (b. p. 40—60°) in needles, m. p. 51·5—52·5° (Jaeger and Smith [5] give 50—52°). The ethynyl group was determined by Hanna and Siggia's method [9] (Found : C, 69·2; H, 7·4; C≡CH, 17·6. Calc. for $C_8H_{10}O_2$: C, 69·5, H, 7·3; C≡CH, 18·1%). Infrared absorption : bands at 3390, 3250, 2130, and 1710 cm.$^{-1}$. The alcohol was fairly soluble in water with neutral reaction and gave no colour with ferric chloride.

The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as needles, m. p. 161° (Found : C, 52·5; H, 4·6; N, 17·7. $C_{14}H_{14}O_5N_4$ requires C, 52·8; H, 4·4; N, 17·6%), absorption max. in $CHCl_3$ at 360 mμ (ε 16,700). The *phenylhydrazone* separated from methanol as needles, m. p. 146° (Found : C, 73·6; H, 7·05. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·05%).

(*b*) *cyclo*Hexane-1 : 2-dione (10 g.) in benzene (100 c.c.) was added dropwise with stirring to the bismagnesium iodide derivative [10] from acetylene [from ethylmagnesium iodide (330 g.) and gaseous acetylene] in benzene (450 c.c.) under nitrogen. After 12 hr. at room temperature the mixture was refluxed for 2 hr. Ice-cold saturated aqueous ammonium chloride (103 g.) was added to the cooled solution, and the organic layer was separated, washed with aqueous sodium hydroxide, dried, and evaporated to an oil (5 g.), distillation of which gave a fraction, b. p. 85°/12 mm. Crystallisation from light petroleum (b. p. 40—60°) gave the 2-ethynyl-2-hydroxy*cyclo*hexanone (2·0 g.), m. p. 53—54° (Found : C, 69·4; H, 7·2. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·3%).

The alcohol (II) was recovered unchanged after treatment with formic acid as described by Chanley [11] and with acid-treated Dowex-50 as described by Newman.[4] Heating for 5—5·5 hr. gave products which were mostly involatile tars, but in each case 1-acetyl*cyclo*hexene (III) (*ca.* 10%), b. p. 65—70°/10 mm., was also obtained (Found : C, 77·1; H, 9·6. Calc. for $C_8H_{12}O$: C, 77·4; H, 9·7%). The 2 : 4-dinitrophenylhydrazone of this had m. p. and mixed m. p. 200—201° (Found : C, 55·1; H, 5·0. Calc. for $C_{14}H_{16}O_4N_4$: C, 55·25; H, 5·3%). Treatment of the alcohol (II) with phosphoric anhydride as described by Saunders [6] also gave 1-acetyl-*cyclo*hexene (25%).

2-Ethynyl-2-hydroxy*cyclo*pentanone,[12] b. p. 86°/12 mm., prepared as described under (*b*), had infrared absorption bands at 3390, 3279, 2101, and 1745 cm.$^{-1}$ and failed to rearrange in formic acid.

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The Dyson Perrins Laboratory, Oxford.
The Queen's University, Belfast. [*Received, June 15th*, 1956.]

[6] Saunders, *Org. Synth.*, 1949, **29**, 1.
[7] Hach, Banks, and Diehl, *ibid.*, 1952, **32**, 35.
[8] Dutch P. 58,279; *Chem. Abs.*, 1947, **41**, 4807; Inhoffen and Kramer, *Chem. Ber.*, 1954, **87**, 488.
[9] Hanna and Siggia, *Analyt. Chem.*, 1949, **21**, 1469.
[10] Bachmann and Chemerda, *J. Amer. Chem. Soc.*, 1948, **70**, 1468.
[11] Chanley, *ibid.*, p. 244.
[12] Dane, Höss, Eder, Schmitt, and Schön, *Annalen*, 1938, **536**, 183.

THE CHEMICAL SOCIETY

'SPECIAL PUBLICATION' NO. 5

To be published December 1956

ANTIBIOTICS AND MOULD METABOLITES

This report of a Symposium held in Nottingham on 26th March, 1956, is the fifth in The Chemical Society's series of Special Publications. The following are the main contributions:—

"Fungal quinones," by J. H. Birkinshaw (London).

"Synthesis of some fungal metabolites," by D. H. R. Barton (Glasgow).

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